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CONTENTS

	PAGE
The Excitatory State. By Dr. W. M. Bayliss, M. A., D. Sc., F. R. S.	347
A Study of Frozen Sections Through a Cadaver Showing The Anatomical Relations of a Large Uterine Myoma. (Illustrated.) By Dr. J. Whitridge Williams	350
The Changes in the Para-Ocular Glands Which Follow the Administration of Diets Low in Fat-Soluble A: With Notes of the Effect of the Same Diets on the Salivary Glands and the Mucosa of the Larynx and Trachea. (Illustrated.) By Shinnosuke Mori, M. D.	357
Note on a Modification of the Chromaffin Reaction, With Observations on the Occurrence of Abdominal Chromaffin Bodies in Mammals. (Illustrated.) By G. B. Wislocki	359
On the Cardiac Complications of Gonorrhœa. (Illustrated.) By W. S. Thayer, M. D.	361
Post-Encephalitic Behavior Disorders in Children. By Leslie B. Hohman	372
Tolerance and Acquired Tolerance of the Mesenchyme Cells in Tissue Cultures for Copper Sulphate and Sodium Arsenite. By Julius Lane Wilson	375
Note on the Abdominal Chromaffin Body in Dogs. By George B. Wislocki and S. J. Crowe	377
Notes on New Books	379

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THE EXCITATORY STATE*

By W. M. Bayliss, M. A., D. Sc., F. R. S.

In this lecture I wish to call attention to certain phenomena associated with the excitatory state or state of activity. At the end of the previous lecture I mentioned the reversible change in protoplasm produced by an electrical shock, in which the liquid sol changes to a jelly with more or less solid properties. The use of the term "gel" has become somewhat indefinite and is sometimes used to mean any kind of precipitation of a colloid. The term "jelly" is sufficiently clear as typified by gelatin when cooled.

Similar changes have been described in cell-division, fertilization and so on, and the method of centrifuging the cell has proved very useful in work of this nature.

A point of interest is that if changes in consistency are indicative of activity, the protrusion of pseudopodia is not active but passive, since the Brownian movements persist. This conclusion does not exclude active contraction elsewhere on the surface, however, and it seems difficult to account for the spherical form of leucocytes when stimulated otherwise than by a contraction of some kind over the whole organism. At the same time, all that the fact really implies is that the surface tension is equal all over.

The chief practical interest of the contractility of protoplasm is in its relation to the properties of the capillary blood vessels, which are essentially protoplasmic. This point will come up again in my next lecture.

Nerve and muscle (including the heart) are commonly regarded as the excitable tissues *par excellence*. But this is due to the fact that their response to stimulus is rapid and obvious. All living tissues are clearly excitable in so far as they respond by change of some

* Second lecture of the Herter Series. Delivered at Johns Hopkins University on March 8th, 1922.

kind to external influences. It is owing to the rapid character of the excitation process in the former tissues that so much investigation has been devoted to it in these cases. There are two aspects of muscular contraction to which I would call attention in connection with the problems of interfaces to which my first lecture was devoted. The first of these concerns the mode of production of the state of tension which the work of A. V. Hill has shown to be the primary fact. His researches have taught us the manner in which the magnitude of a contraction depends on the *length* of the fibres when the contraction begins. This means that the controlling factor is one of surface, not of volume; it is a question of surface energy, not of osmotic energy or of imbibition. The conclusion is confirmed by the results of experiments made to determine the temperature coefficient of the contractile stress. The most accurate and careful work has shown that this is negative; that is, the more powerful contraction is at the lower temperature. As previously mentioned, a surface tension phenomenon is implied thereby. The known production of lactic acid naturally suggests that the deposition of this acid or of its hydrogen ions on the muscle fibrils is the cause of the raised surface tension, as originally suggested by Haber and Klemensiewicz in their classical paper on "Interfacial forces." The presence of lactic acid as the cause of the contractile stress leads to a few remarks on the puzzling facts of "tonus" or "posture" in muscle. It has long been known that smooth muscle is able to enter into a state of shortening in which, as it appears, there is little or no expenditure of energy. This shortening is more or less reduced by rise of temperature; hence again, a surface tension effect is suggested. Since it must be supposed that in the usual form of contraction return to the normal length is associated with removal in some way of the lactic acid which causes the shortening, I have ventured to put forward elsewhere the view that the tonic state might be due to a prolonged remaining of the acid and that some influence may be required to set in action the process which results in its removal. This would be something of the nature of an inhibitory process. Roaf has recently described experiments with a manganese dioxide electrode and finds that in a veratrinized muscle the acidity remains with the shortening, and that when decerebrate rigidity is reflexly inhibited, the acidity decreases. The latter fact shows that the muscle remains acid during the tonic contraction. But the behavior of the manganese electrode is not completely understood. The work of Sherrington on "plastic tonus" has directed attention to the presence in voluntary muscle of phenomena similar to those of smooth muscle. Various researches have shown the existence of certain features in common. I may mention my own work in which the heat production was found to be very small, and that of Roaf which indicates minimal production of carbon dioxide. If the theory of the non-removal of lactic acid, as suggested above, be applied to voluntary muscle, it seems that it would be necessary to assume the existence in voluntary muscle of a distinct innervation process to set in action the relaxation, as in fact is the case with the inhibitory nerves of smooth muscle. This is no doubt a difficulty, but the theory of Bottazzi, according to which tonus is due to sarcoplasmic contraction, does not seem to me to offer a satisfactory solution. It is tempting to connect the sympathetic innervation of voluntary muscle with the tonic state, but it is remarkable how little direct evidence of this has been obtained. The sympathetic innervation remains a mystery.

The second aspect of the excitation process to which I would refer is the increased permeability of the cell membrane which is found to accompany it. The impermeability of the cell membrane in ordinary conditions to most of the ions with which it is in contact is, of course, the reason why living cells have so high an electrical resistance. When the membrane is made permeable, the resistance falls to a notable degree, as in Osterhout's experiments with sodium ions and with anaesthetics. These facts are the basis of Stewart's well known method of determining the proportion of plasma to corpuscles in blood.

I have already pointed out how impermeability to salts may be due to impermeability to one of the ions, the opposite ion being allowed free course, as far as permitted by electrostatic attraction. The result of such a state would be the presence on the outer surface of the cell of an electric charge of the sign of the permeating ion. Suppose that we place electrodes on two distant places of a muscle cell or a nerve fibre, and connect them to some instrument which indicates any potential difference between them, such as the string galvanometer. It has been known for many years that, provided that no injury has occurred, the two points are equipotential. Let us now stimulate one of these places. Our galvanometer shows by its deflection that the two electrodes are no longer equipotential, and further, that the stimulated region is electrically negative to that at rest. Now we know that we have changed the cell-membrane at the stimulated spot into a permeable one, so that the polarization rendered possible by the impermeability to one ion is abolished and the potential difference between the two sides of the membrane at the electrode on the point at rest is no longer opposed, while the direction of the current shows that the outside of the membrane is electropositive to the inside. We have, in other words, by making the excited spot permeable, made the interior of the cell as it were accessible to the leading off electrode. The ions which were arranged in two oppositely charged layers have been enabled to mix together and neutralize their effect. It is not, therefore, that excitation produces

a negative state, but the permeability brought about by it enables the polarized charge at the resting electrode to become evident. This is, briefly, the theory associated with the name of Bernstein, who pointed out that the nature of electrical conduction in solutions necessitated the view that the electrical changes observed in active tissues must be ionic in origin. In support of this conclusion, Bernstein measured the temperature coefficient of the electromotive force of some bioelectrical phenomena and found it to be of the very low value of that of the electrical conductivity of solutions of electrolytes. Some earlier views had associated it with a kind of chemical reaction, which would have had the usual high temperature coefficient of such phenomena. If follows naturally, from what has been said, that if a muscle is in a state of tonic contraction, an inhibition of this state under one electrode would make that spot appear to be positive to that still in contraction. It is of some interest to note that the complex electrical changes described by Orbeli as occurring in the ureter can be interpreted fairly satisfactorily as being due to waves of inhibition followed by waves of contraction similar to those in the intestine preceding and following a mass of food material and propelling it onward (the "law of the intestine" or "myenteric reflex").

My object in calling attention to the electrical phenomena in muscle and nerve is partly also to refer to some points connected with such phenomena as they occur in the heart and in the secreting glands.

But before passing to these, I would mention the work of Starling and his collaborators on the work of the heart muscle. At the beginning of this lecture it was pointed out how A. V. Hill had shown that the magnitude of the contractile tension developed in a muscle fibre depends on the length of the fibre at the initiation of the contraction. Now Starling has demonstrated that the same law holds for the heart muscle and that all the phenomena of the output of the heart in relation to arterial pressure, venous inflow and so on, are to be explained on the basis of the various degrees of filling of the ventricles at the moment of systole. The facts as applied to this organ are embodied in the "law of the heart."

The electrocardiogram is of course a complex case of the electrical change in a muscle fibre as described above, made complex by the fact of the excitation progressing as a wave along an elaborate system of conducting channels. I merely wish to express a doubt as to whether conclusions drawn from changes in the form of the curve have any great significance in relation to the actual working of the heart muscle. We must bear in mind that, owing to the potential difference led off being due to slight differences in the time of arrival of the excitation process at different spots, any state which alters even very little either the rate of the wave in one part or its duration at one spot may exercise a profound influence on the actual form of the "ventricular complex." In the work which was done by Starling and myself on the dog's heart, we were able, by varying the temperature of the air used for artificial respiration, actually to invert the electrical change, without, so far as could be detected, producing any effect on the mechanical beat. The work of Mines and others showed further that, under certain conditions, the mechanical beat could be abolished, while the electrical change remained normal. This merely shows, however, that it is the excitation process that is responsible for the electrical change. Although, according to Einthoven, there may still be a very small contraction, detectable by sensitive methods, the independence in degree of magnitude of the electrical and the contractile change is clear. Again, the form of the "ventricular complex" is sometimes brought into relation with the rapid rate of conduction along the Purkinje tissue as compared with that in the contractile muscle. It has recently been shown that the heart of the chick embryo of 50 hours gives a similar electrocardiogram to that of the adult, although histological examination reveals a structure uniform throughout. Of course, these considerations do not apply to the use of the electrocardiogram in the investigation of block, extra-systole, auricular fibrillation and so on, but it appears to me that great caution is necessary in interpreting varieties of form of the ventricular complex itself.

In conclusion, I wish to refer briefly to the electrical phenomena of secretion, especially in the mammal. It is somewhat remarkable that practically no further work has been done in this region since that of Bradford and myself many years ago. It is now time for a renewed investigation in the light of modern electrical theory. But in the meantime it is worth while to examine how far the facts made out by Bradford and myself are to be explained on the lines of present views of the secretory process. In the first place, it appears that during the period of rest following activity of a secreting gland there is a steady accumulation in the cells of material which is to serve as the precursor of the contents of the secretion. This process is associated with the consumption of oxygen and comes to an end when a certain quantity has been produced. It seems to be controlled by mass action and to proceed automatically, without the intervention of nervous impulses. It is on the whole very similar to the restitution phase of muscular activity. Moreover, like the actual contractile phase of muscle, the act of secretion, when excited by nerve stimulation or by drugs, seems to be independent of oxygen. In the gland, what probably occurs is something like this: the material present in the cell, or some part of it, is split up into smaller molecules, so that the osmotic pressure in the cell rises. This causes attraction of water and momentary distension of the cell. But at the same time that

end of the cell in relation with the lumen of the alveolus and thus with the duct loses its semi-permeability, so that water, carrying with it solutes from the cell, escapes to the duct. Such a current flowing through the cell from the lymph space to the duct continues as long as osmotically active matter together with the permeable state of the one end of the cell remains. The process is similar to the current of water flowing through a tube of sugar solution if the one end is open, the other end closed by a semi-permeable membrane and immersed in water. It was found by Bradford and myself that the electrical change produced in the submaxillary gland of the dog on stimulation of the chorda tympani nerve was definitely associated with passage of water, although the state of knowledge at the time did not permit the more detailed explanation. Now, if the cell membrane of the secreting cell has properties similar to that of the red blood corpuscles, namely, permeability to anions, impermeability to cations, the sign of the electrical difference between the fundus and the duct end of the cell in the excited state corresponds to what would be the case on the hypothesis outlined above. A similar change has recently been found by Anrep and Daly in the pancreas excited by secretin. When the sympathetic supply to the salivary gland is stimulated, there is a small electrical effect in the opposite direction to that of the chorda. The meaning of this requires elucidation. It is important that future work should be done, at all events in the first instance, on dogs, since it is only in these that the effects of the chorda tympani and of the sympathetic supply are clearly differentiated.

A STUDY OF FROZEN SECTIONS THROUGH A CADAVER SHOWING THE ANATOMICAL RELATIONS OF A LARGE UTERINE MYOMA

By J. Whitridge Williams *

In May 1921, Professor Weed informed me that he had received from the Anatomy Board a female cadaver, which he thought might be pregnant. His records showed that the body had come from the morgue, and that the death certificate of the coroner stated that the woman was 26 years old and had died from natural causes.

Upon examination I found the partially frozen body of an apparently middle-aged colored woman, which presented no abnormalities except an abdominal tumor which reached to within three fingers of the xiphoid cartilage, but I could not determine whether it was a pregnant uterus or a tumor of some other kind. It was determined to freeze the cadaver thoroughly and then to section it in various planes in the hope that we might secure information concerning the relations of the pregnant uterus to the rest of the body and particularly to the pelvic floor.

After the body had been thoroughly frozen, the head and the legs were removed, and the trunk was bisected by a sagittal mesial section, which was so accurately made that it involved the pubic joint and the urethral canal. It was then found that instead of a pregnant uterus we had to deal with a lobular myoma, whose largest lobe distended the abdominal cavity, while a smaller lobe completely filled the pelvic cavity, with its lower pole protruding 2 cm. below the line joining the lower margin of the symphysis and the tip of the last sacral vertebra. In other words, the smaller lobe filled out the pelvic cavity and distended the pelvic floor just as a child's head in the second stage of labor before it reaches the vulva.

Two other sagittal sections were made through the right half of the body—one being 3 cm. to the right of the mesial section, and the other 3 cm. to the right of the second. The left half of the body was divided by four oblique sections, which roughly corresponded to the oblique planes which Hodge employed so advantageously in studying the anatomy of the pelvis. The first of these extended through the promontory of the sacrum and the top of the symphysis, while the others were parallel to it and at varying distances below the plane of the superior strait.

Mr. Max Brœdel was kind enough to make tracings of the sagittal sections, from which he prepared the accompanying pen and ink drawings (Figures 1-3). The oblique sections were allowed to thaw in a solution of carbolic acid and formalin and were then photographed. After careful dissection the various landmarks were identified and have been indicated by Mr. Brœdel in the retouched photographs. I take this opportunity to express my sincere thanks for his artistic work, without which this communication would be of but little value, but I am especially indebted to him for his interest and advice during the study and dissection of the specimens.

The object of this communication is to demonstrate the topographical relations of a large myoma and to study the changes which it has produced in the pelvic structures, as well as to show the differences between the distention of the pelvic cavity by a myoma and that resulting from the head of a child at the time of labor. With this in view, I shall briefly describe the condi-

* Lantern demonstration before the American Gynecological Society, May 1922.

tions existing in sagittal sections 1 and 2, then I shall consider the degree of distension of the abdominal and pelvic cavities resulting from the presence of the tumor, as well as the displacement and compression of the abdominal contents. This will be followed by a description of the tumor itself, and the changes produced by it in the ovaries and the uterine ligaments. I shall then take up the consideration of the oblique sections through the left half of the body which illustrate the anatomical distortion produced by the presence of the tumor in the pelvic cavity, and finally I shall study the changes in the vascular supply of the pelvic viscera, as shown in figure 10.

Beginning with the study of the sagittal sections, figure 1, which represents the right side of the vertical mesial section through the trunk, shows that we have to deal with a large myoma whose upper extremity reaches to the level of the twelfth dorsal vertebra and which has compressed and displaced the abdominal and pelvic contents to an extraordinary degree. It is seen that the tumor consists essentially of two main portions—the larger one arising by a comparatively narrow pedicle from the anterior surface of the uterus near its fundus, while the smaller one, which distends the pelvic cavity, arises from the posterior surface of the uterus by a broad pedicle approximately 5 cm. in diameter.

Owing to the distension of the pelvic cavity by the smaller tumor and the upward traction exerted by the larger one, the uterus has been compressed against the symphysis pubis and has become greatly elongated and retroverted. From external os to fundus it measures 16 cm. in length. It is thinnest at the level of the upper margin of the symphysis and thickest just beneath the fundal region, measuring 1 and 2.5 cm. in the two locations respectively. The external os is sharply marked and its anterior lip occupies a somewhat lower level than the posterior, lying approximately 5 mm. above the lower margin of the symphysis. The bladder has been compressed between the uterus and the symphysis pubis in such a manner that its lower portion is represented by a mere slit, while its empty upper half is transformed into an abdominal organ which extends 5.5 cm. above the upper margin of the symphysis. The rectum has been so markedly compressed that only its ampulla and lowermost portion are visible. The intestines have in great part disappeared, and are represented by three small loops, which occupy an irregularly triangular space between the myomatous masses and the fundus of the uterus, and by several loops of transverse colon lying between the stomach and the apex of the tumor.

Anteriorly, in close contact with the lower pole of the abdominal myoma and the upper portion of the uterus, is a small triangular mass, which represents a section through the lower end of the omentum which was adherent to the tumor just to the left of the midline. Before the section thawed, the space between the abdominal wall, the anterior surface of the uterus, and the myoma was occupied by discolored ice, slightly yellowish in hue, and which represented frozen ascitic fluid. Above the upper pole of the tumor it is seen that the abdominal organs are markedly compressed and that all trace of the gastro-intestinal tract has disappeared, except for the contracted stomach and four coils of transverse colon. The liver is in close contact with the under surface of the diaphragm, while the compressed contents of the thorax afford striking evidence of the compression to which the body cavities had been subjected.

Figure 2, which represents the right side of the same section 3 cm. from the midline, shows essentially similar conditions, except that it gives a better idea of the manner in which the larger tumor arises from the fundus, and shows the abundant vascular supply and its extension into the lower pole of the abdominal myoma. In this section the uterus appears thicker than in the midline, and the small vertical slit in its center represents a portion of the uterine cavity. It will be noted that the pelvic cavity is still completely occupied by the pelvic myoma, and in addition that two small myomatous nodules arise from the posterior wall of the uterus and project into the space not occupied by the larger tumor.

Section 3 illustrates the extent to which the body cavity has been distended and the abdominal contents displaced by the tumor. It was drawn after removal of the tumor, which was effected by cutting through its connections with the uterus and separating the various adhesions which fixed its lower pole to the pelvic floor. It is seen that except for the compressed rectum, which is visible only in front of the last three sacral vertebræ, and for the uterus and bladder, which lie just behind the symphysis pubis, the pelvic cavity is entirely empty. Indeed the only structures which can be recognized on casual inspection are the external iliac vessels, which, roughly speaking, indicate the boundary of the superior strait, and the somewhat dilated ureter which extends obliquely downward and forward beneath the peritoneum covering the lateral wall of the pelvis to join the bladder in front of and above the external os.

It is apparent that the major part of the uterus has become an abdominal organ, and, with the few coils of intestines posterior to it, forms a diaphragm which partially divides the body cavity into two portions; the upper of which was occupied by the abdominal and the lower by the pelvic myomatous mass. In the upper cavity it is seen that the tumor was in direct contact with the anterior and lateral abdominal walls, and had displaced the intestines from their usual location, compressing them into an irregular triangular packet which occupies only the posterior and lateral portion of the abdominal cavity. The omentum is greatly elongated and thinned, and extends downward from the lower margin

of the transverse colon for almost the entire length of the abdominal cavity to become eventually attached to the lower-most portion of the largest myomatous mass, just to the left of the mid-line, and to contribute to its nutrition by means of numerous large vessels which it contains.

Figures 8 and 9 represent the anterior and posterior aspects of the tumor, respectively. From these it is seen that the whole tumor, together with the excised upper portion of the uterus, forms an irregular mass measuring 37×20×15 cm., and is made up of three main portions. The upper lobe, which in great part filled the abdominal cavity, is irregularly oval in shape, and measures 22×21×15 cm. in its various dimensions. It arises from the neighborhood of the fundus by a relatively small pedicle. Below it and arising from the right side of the uterus just below the cornu is a pedunculated kidney-shaped myoma, 12×16×4.5 cm. in its various diameters; while the third mass, which fills the pelvic cavity, arises from the upper third of the posterior wall of the right side of the uterus, with its pedicle extending only slightly to the left of the midline. This lobe measures 15×14×11 cm., being greatest in width at its upper portion, while its smaller rounded end was adherent to and distended the pelvic floor. At the junction of its upper and middle thirds a distinct furrow is visible, which has resulted from pressure upon the linea innominata and external iliac vessels. Above this depression the tumor expands on either side, probably as a result of the presence of smaller myomatous nodules within it.

Figure 9, which represents the posterior aspect of the tumor, gives a good idea of the pressure which had been exerted by it, as well as of the compression to which it had been subjected by the various parts. In the upper third of the midline of the pelvic nodule a distinct depression is visible, which corresponds to the location of the promontory of the sacrum; while below it there is a slight convexity which corresponds to the lateral concavity of the hollow of the sacrum. Slightly to the right of this concavity is a broad vertical shallow grove, which has apparently resulted from pressure upon the rectum. Moreover, on the posterior surface of the larger tumor there is a vertical shallow depression which apparently has been produced by pressure against the second, third and fourth lumbar vertebræ, while to the left of this is a narrower, but somewhat deeper, depression indicating the extent to which the aorta had been compressed.

The lower tumor had contracted numerous adhesions with the peritoneum lining the base of the pelvic cavity, which had to be severed before the tumor could be removed. Many of the adhesions were of considerable thickness and contained numerous small vessels, and at first led to some misapprehension when it was attempted to ascertain the relations of the pelvic fascia.

Upon inspecting figure 8 it is seen that the uterus had been deflected somewhat to the right, and had been divided by the sagittal mesial section in such a way that its vertical axis lay just median to the insertion of the left round ligament and the uterine end of the left tube. Moreover, it is apparent that its increased length was in great part due to hypertrophic elongation of the supravaginal portion of the cervix, while the cavity of its body was little, if at all, increased in size.

Owing to the fact that the pelvic cavity was completely filled by the lower myomatous mass and that the uterus had been drawn far up into the abdominal cavity by the traction exerted upon it by the larger tumor, the tubes and ovaries have become abdominal organs, while the anatomical relations of the round ligaments have been profoundly altered. The median ends of both tubes are approximately normal. The lateral portion of the left tube is adherent to the external surface of the left ovary and is so compressed as to be recognized with difficulty. Its fimbriated end, however, is free and can be identified by a long ovarian fimbria, which is attached to the external surface of the upper pole of the corresponding ovary. The right tube, except for its abnormal location, is apparently normal and at its lateral end is in contact with the flattened-out ovary. This measures 6.5×4.5×0.5 in its various diameters, and presents a convex external and a concave internal surface, as the result of its compression between the tumor and the abdominal wall.

The ovarian ligaments are normal in size and except for their upward course present the usual relations. But for the fact that they are situated far above the pelvic brim, the infundibulo-pelvic ligaments, likewise, show nothing unusual except the presence of unusually large vessels. Upon laying back the peritoneum, the ovarian vessels were exposed, when it was found that the arteries were extremely tortuous and convoluted and measured 5 mm. in diameter. The veins were made up of numerous branches which had eventually united to form a single trunk. On the left side this occurred at the level of the fourth lumbar vertebra, above which the single vessel presented a diameter of 12 mm.

Owing to the distortion produced by the tumor the relations of the round ligaments on the two sides vary greatly. As shown in Fig. 8, the right ligament presents essentially normal relations, while the left has undergone great distortion. The former is comparatively short, and consists of a uterine portion 4 cm. long, and a terminal portion of about the same length, which occupies the right inguinal canal and terminates in the upper part of the labium majus. The latter, on the other hand, is greatly elongated and measures 22 cm. in length. Instead of extending upward, forward and outward to reach the internal ring, it extends downward and backward from its uterine origin to penetrate the perito-

neum at a point 10 cm. posterior to the midline and 4.5 cm. above the level of the superior strait. It then turns and pursues a downward and forward course beneath the peritoneum, to disappear in the mons veneris, 4 cm. to the left of the midline.

As has already been indicated, the uterus has in great part become an abdominal organ, so that 11 cm. of its length lies above the level of the superior strait. Upon dissecting the broad ligament and the adjacent structures, it is found that the peritoneum forming the utero-vesical sac can be separated from the anterior surface of the uterus to within 4.5 cm. of its fundus, above which further separation is impossible. As figure 1 shows that this is considerably above the apex of the bladder, it gives an idea of the extent to which further distention of that viscus could occur.

Our description thus far applies in great part to the general topography of the tumor and to the effect which it had exerted upon the economy of the woman. On the other hand, information of more particular gynecological and obstetrical interest may be gained from the study of the sections through the left side of the body which were made parallel to the superior strait.

Fig. 4 represents a retouched photograph showing the relations at the superior strait. The section passes through the top of the symphysis and the cartilage covering the promontory of the sacrum, and extends upward and backward to the skin of the back in such a way as to involve the body of the fifth, the arch of the fourth and the spinous process of the third lumbar vertebra. It corresponds to Hodge's first oblique plane and shows clearly the extent to which the soft parts encroach upon the pelvic inlet.

The pelvic cavity is completely filled by the myomatous mass, which has pushed the uterus so far forward that it is separated from the posterior surface of the symphysis only by the compressed slit-like bladder. It is interesting to note how large a portion of the ilio-psoas muscle occupies the iliac fossa, as well as the fact that the external iliac vein follows practically the contour of the linea innominata, but is in contact only with its anterior and posterior ends. It should be noted that the triangular space just lateral to the body of the first sacral vertebra is occupied by the hypogastric artery and vein, the ureter and by the obturator nerve. Anteriorly, it is seen that the uterine body is directly in contact with the bladder and so compressed that it does not exceed 1 cm. in thickness. The broad ligament extending from its margin is greatly thinned out and lies in contact with the anterior and lateral walls of the pelvis, instead of extending transversely across the middle of the pelvis, and dividing it into an anterior and posterior pocket. It should further be noted that the anterior face of the broad ligament lies in contact with the pelvic fascia, that the double fold of peritoneum which should normally be present has disappeared; while the peritoneum covering its posterior face constitutes the peritoneal lining of the anterior portion of the pelvis. In other words, the myoma occupies the immensely distended pouch of Douglas, and has displaced and compressed everything in front of it.

Fig. 5 represents a section parallel to, and two centimeters below, the superior strait. It bisects the symphysis pubis and the body of the first sacral vertebra, while posteriorly it involves the arch of the fifth and the spinous process of the fourth lumbar vertebra. It will be noted that the bony ring of the pelvis is here complete, being formed posteriorly by the body of the sacrum, laterally by the iliac, and anteriorly by the pubic portions of the innominate bone.

The sacro-iliac joint is well shown, and it is apparent that in this instance the sacrum does not form the keystone of an arch, but would prolapse into the pelvic cavity under the influence of the body weight were it not held in place by strong ligamentous structures. It is likewise apparent that the myoma completely fills out the pelvic cavity and has led to intense compression of the uterus, which at this level is represented by a cross-section of the flattened cervix. The broad ligament is much thinner than in the preceding section and lies in direct contact with the thinned-out lateral ligament of the bladder, which extends outward from the margin of that viscus.

Probably the most striking feature in this section is the presence of a small segment of the ilio-psoas muscle, which has descended beneath the level of the linea innominata and actually encroaches upon the pelvic cavity. The distended ureter in its course towards the bladder has come to occupy the middle of the lateral pelvic wall and is separated by the pelvic cavity only by peritoneum and sub-peritoneal fascia. The various arteries and veins are well shown, and passing down over the anterior surface of the lateral mass of the sacrum is the lumbo-sacral trunk. In this section it is apparent that, while the ureter lies median to the pelvic fascia, the main vessels in the posterior segment of the pelvis are enclosed within sheaths derived from it. It is important to note that in this section there is as yet no sign of the obturator internus, the pyriformis or the levator ani muscles.

Fig. 6 represents the upper surface of the third parallel section and lies 2.5 cm. posteriorly and 3 cm. anteriorly below the section just described. This plane bisects the second sacral vertebra, while its anterior end terminates in the external genitalia half a centimetre below the lower margin of the symphysis. For practical purposes it corresponds with Hodge's second parallel plane and with Veit's main plane of the pelvis, and would be identical with the latter did its ends involve the lower margin of the first sacral vertebra and symphysis pubis respectively. Here it will be noted that the bony wall of

the pelvis is no longer complete, its anterior portion being represented only by the descending ramus of the pubis, to whose left lie the erectile structures just beneath the pubic arch; while to the right is the obturator foramen, which is covered internally by the median end of the obturator internus muscle.

The sacro-iliac joint is well shown, and it will again be noticed that the sacrum represents an inverted keystone of an arch, and that only a fraction of its thickness takes part in the formation of the joint. Laterally, where the innominate bone is sharply constricted and is devoid of cancellous tissue, is a plate of compact bone which corresponds to the apex of the sacrosciatic notch. In this section it is again evident that the pelvic cavity is completely occupied by the myomatous mass. Anteriorly, the uterus has disappeared and has been replaced by the vagina. Attention is directed to the fact that the thinned-out broad ligament of the previous sections has given place to its thick vascular base and to the perivaginal tissues. The former lies internal to the lateral vesical ligament, and gradually fades away as the middle portion of the pelvic wall is approached. Furthermore, it should be noticed that the uterine artery has receded from the midline, and, roughly speaking, occupies a position opposite the lateral margin of the obturator foramen.

Anteriorly and laterally, the obturator internus muscle is seen as a thin structure varying from 2 to 5 mm. in thickness, extending from the ischio-pubic ramus to the ischial spine, and giving no suggestion of the dimensions it will assume in the next succeeding section. In the posterior quadrant of the pelvic cavity, and lying in front of the sacro-iliac joint, the sacral plexus may be seen approaching the sacrosciatic notch. It lies external to the pelvic fascia and is separated from the bone only by the superior gluteal vessels, and its location affords a ready explanation for at least some of the pain, which may be associated with relaxation of that joint. In the extreme anterior and median portion of the section the labium majus and minus are visible, while posterior to them lie the various erectile tissues associated with the clitoris.

Fig. 7 is very instructive and gives a conception of the topography of the pelvis which cannot be gained by the ordinary methods of study. This section, which is parallel to the preceding one, lies 2.6 and 2.8 cm. beneath its posterior and anterior ends respectively. Posteriorly it extends through the tip of the third sacral vertebra, while its anterior portion involves the external genitalia and is obliquely traversed by the urethra just beneath its upper surface. The tumor still occupies the greater part of the pelvic cavity, but the striking features of the section are afforded by the relations of the pelvic muscles, the sciatic nerve and the base of the broad ligament. At this level it is seen that the obturator internus has become transformed from the thin structure visible in the previous section into a thick-bellied muscle, which extends from the descending pubic ramus to the ischial spine while external to the body of the ischium its strong tendon can be seen on its way to its point of attachment in the depression at the back of the trochanter.

The pyriformis muscle presents a striking picture and appears as a surprisingly large structure, which arises from the greater part of the anterior surface of the sacrum, and passes through and almost completely fills the sacro-sciatic notch on its way to its attachment to the femur. Internal to the obturator internus can be seen an oblique section through the levator ani muscle, which at this level varies between 3 and 4 mm. in thickness. It can be traced upward for about half a centimetre into the preceding section, where its insertion to the posterior surface of the symphysis and ischio-pubic ramus, to the white line, and to the ischial spine can be located. In this section the muscle is covered on either surface by fascia, while above the two layers fuse into the single layer of pelvic fascia above the white line. Under normal conditions in this location the peritoneum covering the internal layer of fascia over this muscle should line the entire pelvic cavity, but in the specimen under consideration a thick layer of abundantly vascularized pelvic connective tissue is interpolated between it and the pelvic cavity. In other words, the anterior segment of the pelvic cavity has become obliterated, while Douglas' cul-de-sac has become greatly expanded.

In this section, likewise, we see the sciatic nerve in oblique section, which affords a vivid picture of its magnitude and teaches us how readily its median end can be subjected to pressure by an object distending the pelvic cavity. Just anterior to the nerve and almost in contact with the ischial spine can be seen the internal pudic vessels. On inspecting the anterior portion of the section, the vagina is represented by two slits, which are directed obliquely backward and are separated by a thick layer of highly vascularized tissue. This is the result of an oblique section through a fold of its mucosa, and by no means indicates that the canal is double. Posteriorly the sacro-iliac joint is again seen, and once more it shows that the union at the sacro-iliac joint is such that, if the sacrum were not held in place by strong ligamentous structures, it would inevitably collapse into the pelvic cavity.

This section represents almost the base of the pelvic cavity; for in the next one, which lies 3 cm. beneath it and extends through the tip of the fifth sacral vertebra, all that is left is a shallow oval area about 5.5 cm. in diameter, and 5 mm. in depth, lying immediately over the coccygeal vertebræ. Posteriorly, this depression is occupied by peri-rectal tissue which is abundantly supplied with vessels, while anteriorly and laterally the thinned-out margins of the levator ani can be distin-

guished, whose fibers fuse with and disappear into those of the sphincter ani. The greater portion of this last section, which is not figured, is made up of an oblique section through the gluteal muscle, outside of which comes a layer of subcutaneous fat which varies from 2 to 5 cm. in thickness.

Upon dissecting the lower surface of the fourth section from below, the ischiorectal fossa can be opened up as a large potential cavity bounded internally by the levator ani and its fascia, and externally by the layer of fascia covering the obturator internus, the pyriformis and the gluteal muscles, and reaching its apex at the level of the white line.

Thus far, we have studied the relations of the tumor to the pelvic cavity and to the structures within it. Incidentally, we have mentioned the enlargement of the ovarian vessels and those of the broad ligament, and we shall now study the changes which have occurred in the vessels supplying the pelvic organs. These are best studied in figure 10, which represents the lateral wall of the pelvic cavity after the removal of the tumor, as seen in a sagittal section through the right side of the body, 3 cm. from the median plane. The striking features of this section are the relations of the ureter and of the pelvic vessels. The former is dilated to several times its usual calibre and constitutes a hydro-ureter. Posteriorly the vessels present essentially normal conditions, while anteriorly they show numerous deviations from the usual relations which have resulted from the presence of the tumor and the consequent need for an increased vascular supply.

The median surface of the section involves the lowermost end of the common iliac vein just before it divides into the external and internal iliac veins. On the other hand, the point of division of the artery lay higher up and median to the plane of the section, so that the external and internal iliac arteries appear as separate vessels.

The external iliac artery and vein need not concern us here, as they have already been considered in connection with Fig. 4, where the latter formed the outer boundary of the superior strait. The internal iliac or hypogastric vessels are, however, of great importance. Shortly after entering the pelvic cavity the hypogastric artery divides into three main branches. The outer one continues forward, upward and eventually inward toward the umbilicus, as the obliterated hypogastric artery. The median branch is the uterine artery which is unusually elongated and enlarged. After passing beneath the ureter, it follows the pelvic wall as a vessel with many convolutions almost to the symphysis pubis where it enters the base of the broad ligament to supply it and the uterus, instead of entering it at about the middle of the pelvis. The posterior division is the largest of the three, and is much larger than under usual conditions. After traversing the posterior portion of the pelvis for several centimeters, it divides into the inferior gluteal and the middle and inferior hemorrhoidal arteries.

Thus it is seen that except for a considerable increase in the size of all vessels and the striking elongation and tortuosity of the uterine artery, the arterial supply of the pelvis differs but little from normal. On the other hand, the venous supply has become extraordinarily expanded, and the section clearly shows that the lateral pelvic wall is covered by a number of large trunks, each of which approximates the external iliac vein in size, and which extend from the anterior portion of the pelvic cavity in order to carry away the blood from the enlarged uterus and its appendages. It is evident that they here form a plexus, which has attained immense proportions and covers the entire middle third of the lateral and anterior pelvic walls, and which drains the vesical and utero-vaginal regions. Posteriorly, just in front of the pyriformis muscle, the lumen of an immense vein is visible which has probably resulted from the union of the gluteal and hypogastric veins.

This picture was obtained by turning back the peritoneum and the subperitoneal fascia, and shows that all of the vessels in question were surrounded by their own fascial sheaths and lay median to the main pelvic fascia, so that, in their anterior portions at least, they were separated from the levator ani muscle by that structure. In the lower part of the section a small segment of the rectum is seen, whose anterior and upper wall has been deflected in order to expose the vessels beneath it. This section likewise affords an excellent picture of the relation of the muscles of the pelvis. Anteriorly, the obturator externus and obturator internus muscles are seen upon the two aspects of the obturator fascia, respectively. Median to and in close contact with the obturator internus, the anterior half of the levator ani muscle is seen, which with its posterior portion forms a diaphragm concave above and convex below, which extends from the horizontal ramus of the pubis to the ischial spine. In this section the muscle scarcely exceeds 1 mm. in thickness and is considerably thinner than in Fig. 7; while in its anterior portion, immediately adjacent to the bone, it is almost fascial in character. Over-lapping its posterior extremity and lying external to it, a section through the coccygeal muscle is visible, which is only a fraction as extensive as the levator. Still further posterior and higher up, a section of the pyriformis is seen in the shape of a large triangular muscular mass lying between the anterior and inferior end of the sacral ala and the upper and anterior surface of the gluteus maximus muscle. In front of the pyriformis are the lower two, and above it and in contact with the anterior surface of the sacrum are the upper two, of the four spinal roots of the sacral plexus; while at the uppermost por-

tion of the anterior surface of the sacrum a section of the lumbo-sacral trunk is visible. This is in marked contrast with the appearance of the sacral plexus as shown in Fig. 7, and illustrates the conditions more median to its point of origin. In front of the pyriformis muscle the internal pudic artery can be seen making its way toward the ischial spine on its course to the external genitalia.

This completes in a cursory way the description of what the various sections show, and it only remains to recapitulate in a few words the changes brought about by the presence of the tumor and to compare the behavior of the pelvic floor with what would have resulted had the pelvis been distended by a fœtal head late in labor.

In the first place, the specimen gives an extraordinarily accurate idea of the extent of the abdominal and pelvic distension which may be produced by the presence of a large myoma. Owing to the fact that the nodule, which almost completely filled the pelvic cavity, arose from the posterior surface of the uterus, the distention has occurred altogether posteriorly to that organ, with the result that it together with the bladder has been compressed against the anterior pelvic wall.—In other words, the distention has occurred entirely within the pouch of Douglas. This has resulted in a remarkable displacement of the broad ligaments, so that they are in contact with the anterior and lateral wall of the pelvic cavity instead of dividing it into an anterior and posterior segment; the former has become obliterated and the latter immensely distended. Owing to the forward displacement of the uterus and of the median ends of the broad ligaments, great elongation of the uterine arteries was necessary. This apparently has occurred to an even greater extent than was essential, as is shown by the fact that instead of entering the base of the broad ligament shortly after they have been crossed by the ureters, the arteries extend forward almost to the symphysis pubis before so doing, and at the same time have become unusually convoluted. Moreover, even though myomata are in general very poorly vascularized, the demands for the nutrition of the tumor have necessitated an increase in the blood supply, as is shown by the unusual hypertrophy of the pelvic veins, which has attained a degree encountered only in full-term pregnancy.

Upon comparing the changes in the pelvic floor in this instance with those occurring during normal pregnancy, several very important points of difference should be noted. In the first place, when the pelvic cavity is occupied by the fœtal head late in the second stage of labor, the distension proceeds from a central point, with the result that the cervical canal together with the base of the broad ligament becomes expanded outwardly in all directions, to an equal extent, so that while the anterior and posterior peritoneal pouches are temporarily obliterated, no such change occurs as was noted in this instance. In it the pelvic tumor lay behind the uterus, and consequently, as it increased in size, the posterior pouch became immensely distended, while the anterior pouch was obliterated by the cervix being pressed firmly against the symphysis pubis. At the same time the broad ligaments were flattened out against the anterior and lateral portion of the pelvic wall, instead of involving its posterior segment as well. The distension has likewise led to comparable changes in the relations of the pelvic fascia and the structures beneath it, which, instead of being pushed centrifugally outwards from a common center, have become distended only posterior to the uterus, with the result that the levator ani muscle forms a continuous but thin pelvic diaphragm, instead of being perforated and pushed downward and outward to form the lower-most portion of the birth canal.

Finally, particular attention is directed to the unusual picture of the anatomical relations which have been obtained by the employment of oblique sections through the pelvis parallel to the superior strait, and which indicate the advantages which might well follow the use of similar sections in the study of the dislocation of the pelvic floor during labor, as well as in the study of the part played by the bases of the broad ligaments in the maintenance of the normal position of the uterus in the non-pregnant woman.

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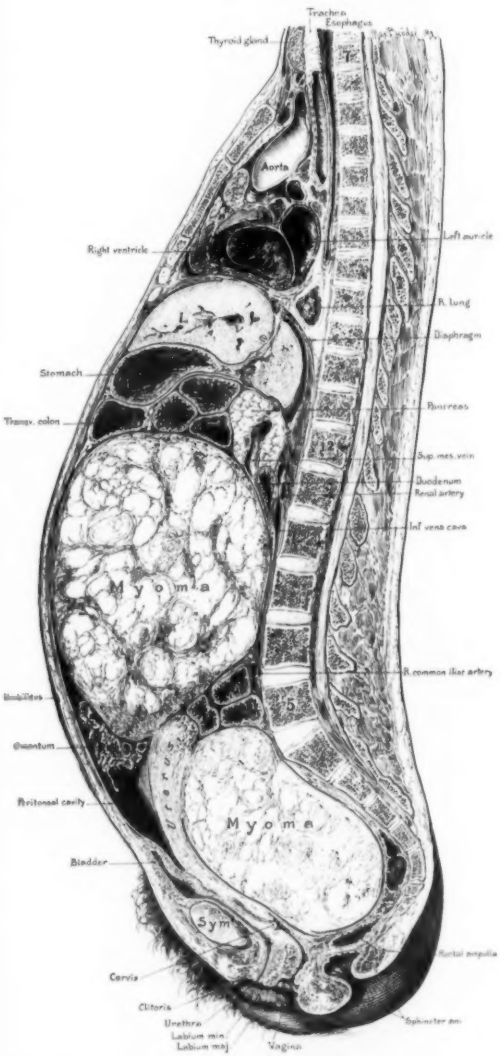


FIG. 1.—Sagittal mesial section, showing relations of tumor and displacement of viscera. × 1/4.

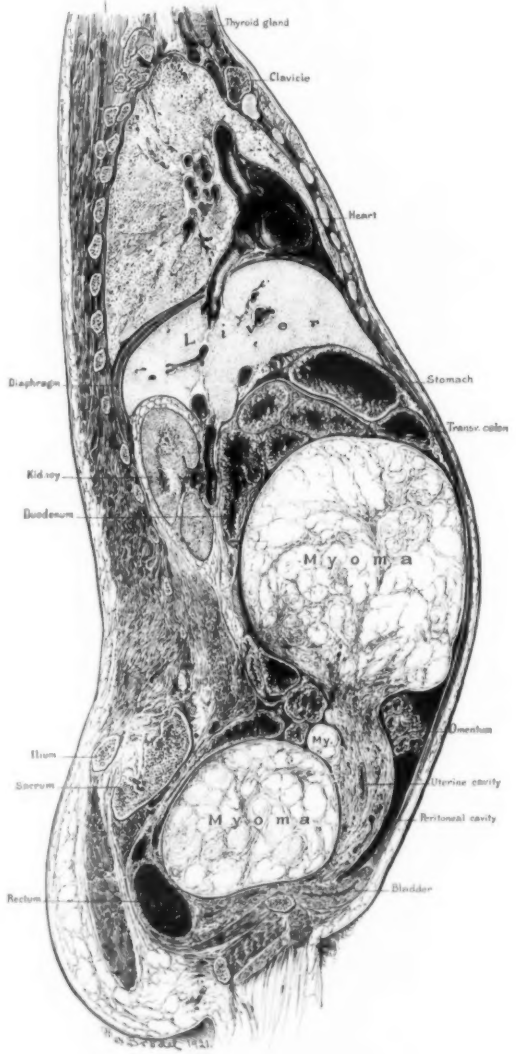


FIG. 2.—Reverse side of figure 1, 3 cm. to the right of midline, showing relations of tumor, and particularly the connection between the abdominal nodule with the fundus uteri. × 1/4.

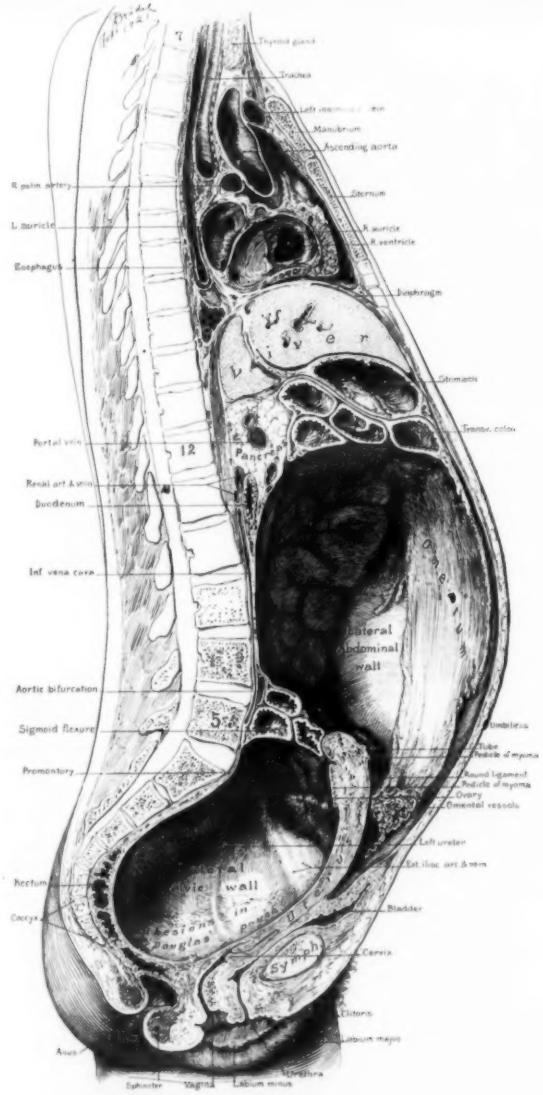


FIG. 3.—Sagittal mesial section, showing left half of the body after removal of tumor, illustrating the distension of the abdominal cavity and the displacement of the pelvic viscera. Note the compression of intestines and the elongation of omentum. × 1/4.

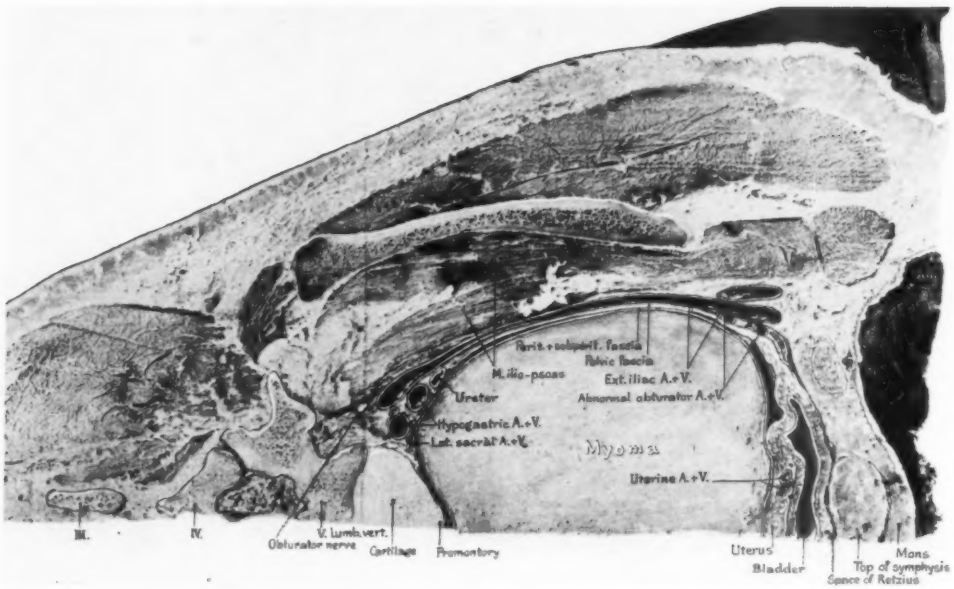


FIG. 4.—Oblique section through left half of body, showing relations at plane of superior strait. × 1/2.

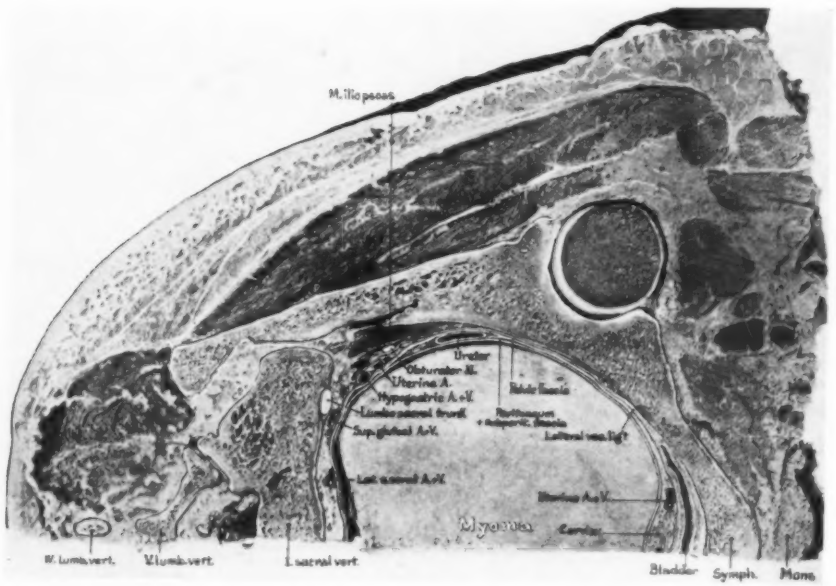


FIG. 5.—Oblique section parallel to and 2 cm. below that shown in figure 4. To demonstrate absence of pelvic muscles in this area. × 1/2.

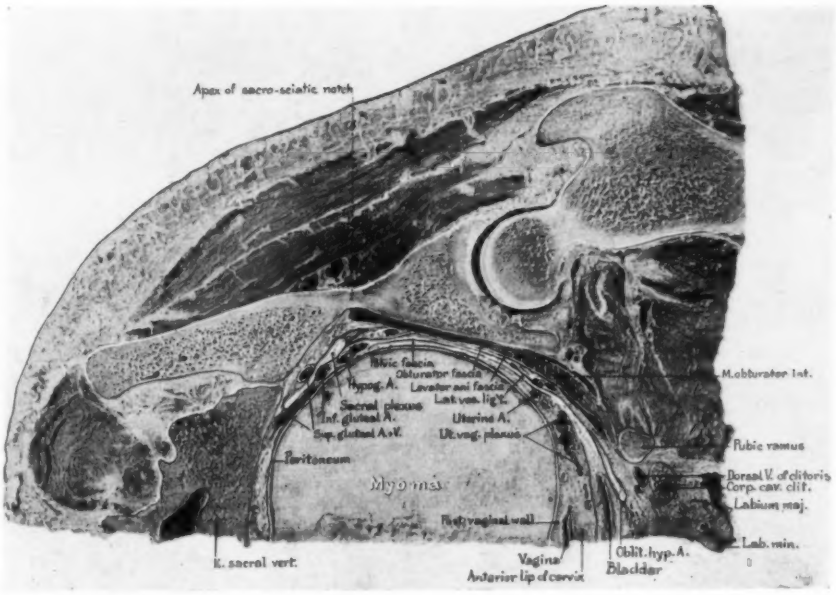


FIG. 6.—Oblique section through left half of body, parallel to and 5 cm. below that shown in figure 4. (Hodge's second parallel plane). × 1/2.

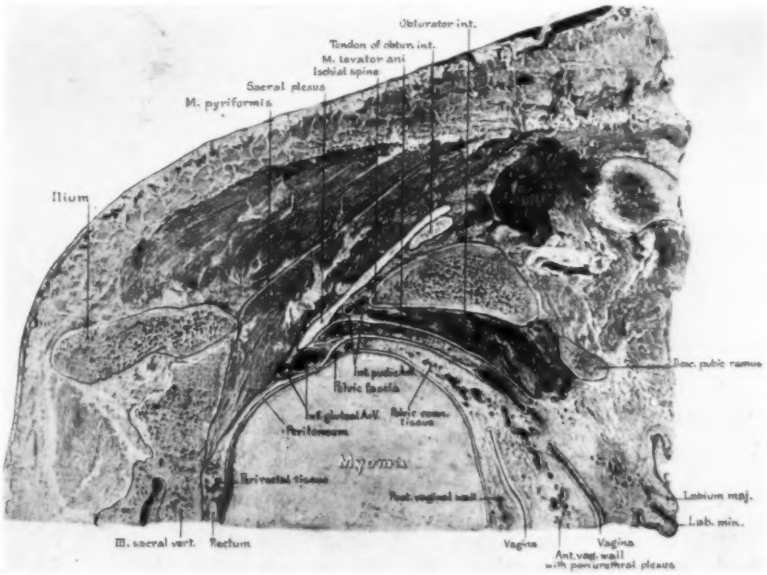


FIG. 7.—Oblique section parallel to and 2.5 cm. below that shown in figure 6, extending through the tip of the third sacral vertebra. To illustrate the extent of the pelvic musculature. × 1/2.

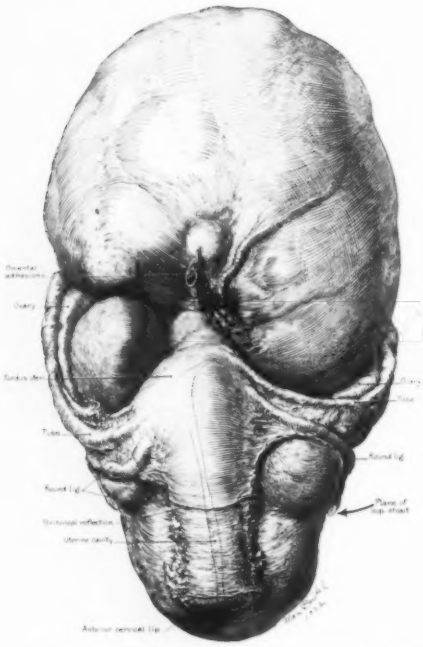


FIG. 8.—Anterior view of tumor showing its relations to the uterus, round ligaments and tubes. × 1/3.

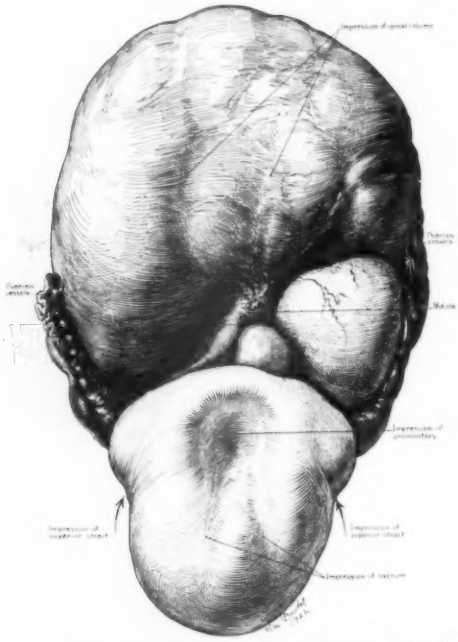


FIG. 9.—Posterior view of tumor showing indentations due to pressure exerted by the margins of the superior strait and vertebral column. × 1/3.

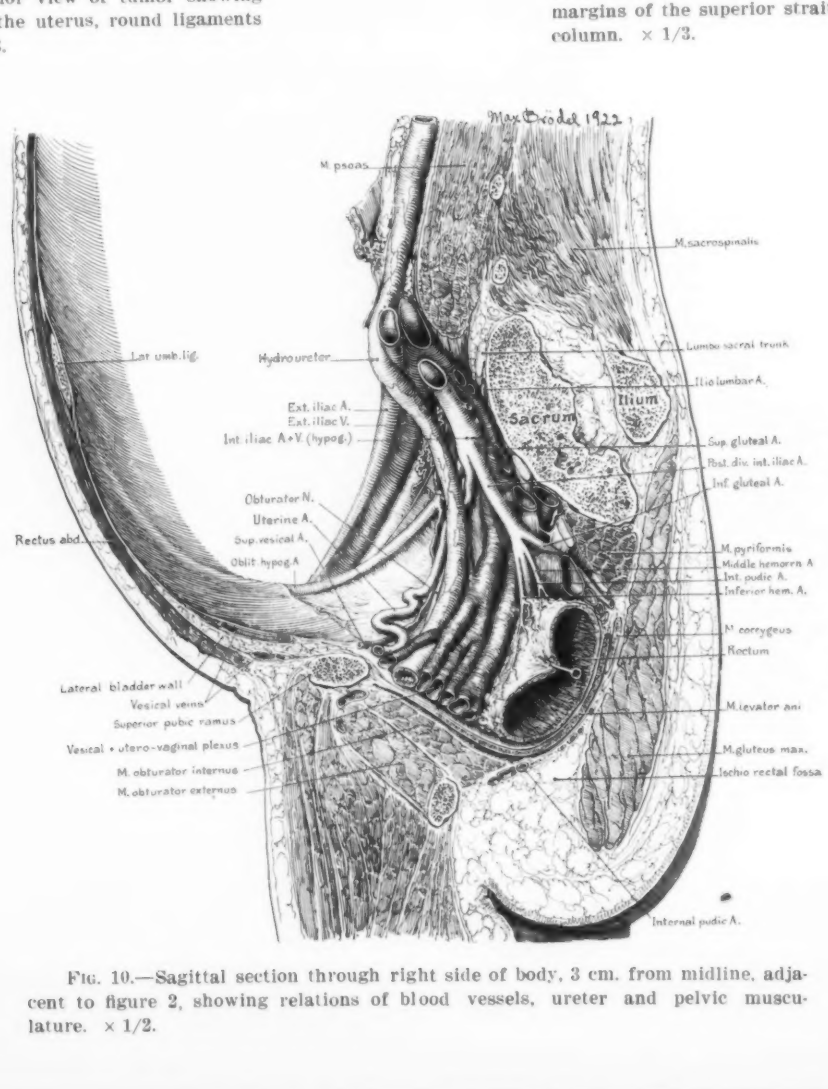


FIG. 10.—Sagittal section through right side of body, 3 cm. from midline, adjacent to figure 2, showing relations of blood vessels, ureter and pelvic musculature. × 1/2.

THE CHANGES IN THE PARA-OCULAR GLANDS WHICH FOLLOW THE ADMINISTRATION OF DIETS LOW IN FAT-SOLUBLE A; WITH NOTES OF THE EFFECT OF THE SAME DIETS ON THE SALIVARY GLANDS AND THE MUCOSA OF THE LARYNX AND TRACHEA

By SHINNOSUKE MORI, M. D.

Chief of the Ophthalmological Clinic at the South Manchuria Railway Company Hospital, Dairen, Manchuria

(From the Department of Chemical Hygiene, School of Hygiene and Public Health, Johns Hopkins University, Baltimore)

In a previous paper[1] I showed that the primary changes which occur in the eyes of rats on diets deficient in fat-soluble A are xerosis conjunctivæ, and xerosis corneæ (xerophthalmia). These changes are identical with those of xerosis in human eyes which are believed to result from dryness of the tissue. The ulceration and destruction of the cornea which follow xerosis corneæ and conjunctivæ (keratomalacia) are due to the secondary infection of the cornea by micro-organisms. Since the primary change in these tissues is due to dessication, it would seem logical to look for the cause of the trouble in the organs whose secretions under normal conditions serve to moisten the conjunctival sac. The secretion of the lacrimal gland—the tears—is chiefly concerned with the moistening and cleansing of the surface of the anterior portion of the eye. Beside the secretion of the lacrimal gland the conjunctival sac receives that of the Meibomian (tarsal) glands in the lids. The Harderian gland in the orbit also pours its secretion into the conjunctiva, and the mucous cells in the membrane itself contribute also to the conjunctival fluid. All these secretions are mingled in the conjunctival sac, and the resultant mixture moistens and protects the eyeball. The anterior part of the eye is kept clean by this secretion in which there is a more or less constant current, running toward the nose, which serves to wash foreign material through the naso-lacrimal duct. This fluid also checks the multiplication of micro-organisms, since the tears possess some bactericidal power. How effective this mechanism is in removing bacteria from the conjunctival sac may be judged by the fact that bacteria, after being sprayed into the conjunctival sac, may be recovered from the nose in five minutes.[2] The purpose of this paper is to report the changes which occurred in the above-mentioned glands from animals in various stages of experimentally induced xerophthalmia. Moreover, I have also attempted to correlate the changes in these para-ocular glands with those in the salivary glands, and the changes in the conjunctiva with those in the mucosa of the larynx and trachea.

Lacrimal gland.—The most striking change in the tissue of this gland in animals suffering from xerophthalmia is in shrinkage of the secretory cells of the acini. These cells become very much shrunken. They no longer show secretory zones. The nuclei take on irregular shapes, occupy the central part of the cytoplasm, which is very small and stains very poorly. The individual acini of the gland become so small that it is impossible to distinguish them with the low power of the microscope, and the gland appears to be a simple mass of nuclei. It is not to be expected that a gland in this condition can produce tears. In a certain number of animals the cytoplasm of the gland cells is occupied by very large vacuoles to such an extent that the bioplasm itself has almost disappeared. The nuclei of such cells are small, centrally located and deeply stained. Frozen sections stained with Sudan III and sections from material which has been fixed in Fleming's solution show that some of these apparent vacuoles are in reality droplets of fat. Glands such as I have described are those which are most severely affected, but even in those that are most nearly normal, the cells show no evidence of pre-secretory or secretory activity; they are clear and small, and do not stain well. The poorly stained nucleus is situated in the basal portion of the cell, surrounded by small vacuoles in the cytoplasm, whose central portion consists only of a fine network. Although it is possible that such cells may produce some secretion it is quite certain that the production would be in very much diminished quantity.

The above findings indicate that the lacrimal glands of animals affected with xerophthalmia produce little, if any, secretion; in any case it is difficult to believe that any secretion which they might produce could be normal. It is quite certain that some of these glands have ceased secreting entirely.

Meibomian gland.—Sections of the lids of the eyes of animals suffering from xerophthalmia very often show cystic dilatation of the ducts of the Meibomian glands. These cysts are filled with fat—the secretion of the gland cells. The epithelium of the margin of the lid shows

evidence of a very marked xerotic process, and the same change is found in the epithelium of the duct. It is very likely that this xerosis may play a part in the occlusion of the duct and the formation of the retention cysts.

Harderian gland.—The lumina of the acini of this gland may be either very much dilated and empty, or narrowed by swelling of the secreting cells. Frozen sections of this gland show a remarkable diminution of the fat content of the cells and the lumen. The connective tissue about the gland acini is very often densely infiltrated with round cells.

The mucous cells of the conjunctiva are all entirely destroyed in the course of the xerotic process.

It is quite certain from these findings that the entire secretory apparatus of the eyes of these rats is in a state of dysfunction, that is, the secretion from these glands is either very much diminished or entirely lacking. The changes in the lacrimal gland are the most important in the pathological picture of this disease, and in fact the changes in this gland would seem to be the cause of the lesions in the cornea and conjunctiva. The diminution or the lack of the secretion of the lacrimal gland would explain the dryness of the eyeball as well as the xerosis of the cornea and the conjunctiva. The failure of the lacrimal secretion would, moreover, explain the increase in number of the organisms found in the conjunctival sac.

Salivary glands.—Having found very evident changes in the lacrimal gland during the course of xerophthalmia, it seemed logical to study the salivary glands which both in nerve supply and in structure resemble the lacrimal glands very closely. I therefore made a comparative study of these glands in rats affected with xerophthalmia. The glands of normal and of xerophthalmic animals were fixed in 10% formalin, or in Fleming's solution, embedded in celloidin, or cut in frozen sections and stained with hematoxylin-eosin, iron hematoxylin, safranine, and Sudan III.

The submaxillary and parotid glands of the rat are serous; the sublingual is a mucous gland. In many rats with xerophthalmia either all or some of these glands are either not secreting at all or secreting very little. The secreting cells become much shrunken. The acini are very small and show no traces of secretion. The epithelium of the intra-lobular ducts is shrunken and the cells are irregular in size.

The epithelium of the principal ducts of these glands often shows a remarkable degree of cornification and desquamation of the thickened superficial cells, so that the lumen of the duct becomes narrow and is often occluded. These changes resemble the xerotic changes in the eye. In two cases the occlusion of the ducts of the sublingual gland was followed by the dilatation of the duct and the gradual atrophy of the gland cells. Dilatation of the small ducts occurs frequently in the parotid gland. Coincident with the xerotic changes and those in the parenchymal cells, the ducts are invaded by bacteria and small abscesses are formed in the gland. In other words, the findings in the salivary gland are of a nature similar to those in the lacrimal gland, and the duct epithelium undergoes a change which is identical with those which occur in the conjunctival epithelium. The reason for the infection of the salivary glands in these animals probably explains also the parotitis which sometimes complicates typhoid fever. The glands are directly infected from a dry mouth which contains an abnormally large number of micro-organisms.

The other secretory organs, such as the liver, pancreas, bowel, kidneys, thyroid, showed no remarkable change in sections except in one case. In this animal the cytoplasm of a small number of cells of the pancreas was very much vacuolated. The reproductive glands of rats on a xerophthalmia-producing diet do not function. Reproduction in these animals almost never occurs. Wason [3] has reported fibrosis of the testes in two animals which she examined after they had been on a xerophthalmia-producing regimen.

Clinically and at autopsy, the mucous membrane of the mouths of these rats was very dry. The animals thus afflicted in the early stage of the disease sneeze and cough violently, but later the cough subsides spontaneously and after a period of dyspnœa the animals die. Nevertheless, histological sections of the mucosa showed no more than the normal cornification of the epithelium. On the other hand, the mucous membrane of the larynx and trachea showed xerotic changes. The normal epithelium of the larynx and trachea is ciliated columnar in type, except that of the vocal cords, which are covered with stratified epithelium. The xerotic changes first appear in the epithelium of the larynx. The outer layer of cells in this region becomes cornified and stains deeply with eosin. The cells lose their nuclei, and become much flattened. In the second layer typical granules of kerato-hyaline appear. The epithelium becomes much thickened and is often infiltrated with pus cells. Gradually this xerotic change involves the tracheal mucosa. Xerosis then becomes complicated by an inflammatory process which often involves the bronchi and lungs and may terminate in a bronchopneumonia. Such a pneumonia was responsible for the death of most of the animals which were not sacrificed. The mucous cells in the mucous membrane are completely destroyed. Those which are embedded in the submucosa show evidence that their secretion is either diminished or that their secretory power is entirely destroyed. It is easily seen from the foregoing description how closely these changes in the mucosa of the larynx and trachea resemble those in the cornea and conjunctiva. If the same conditions obtain in the larynx and trachea as in the conjunctival sac, the bacterial content of the air passages should be much increased

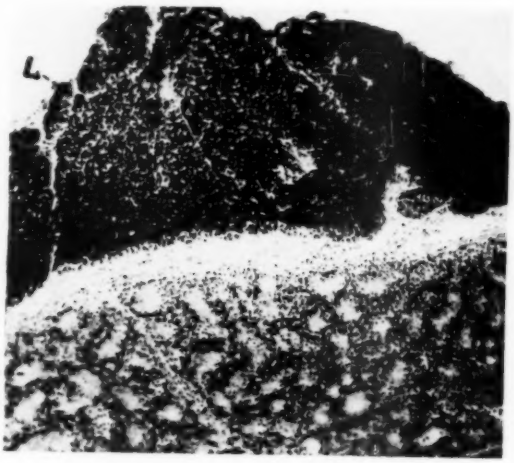


FIG. 1

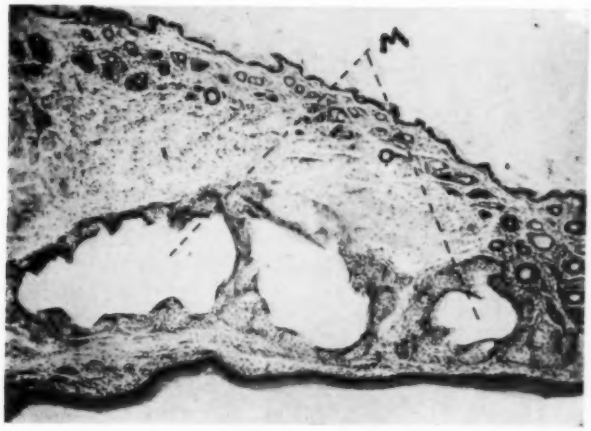
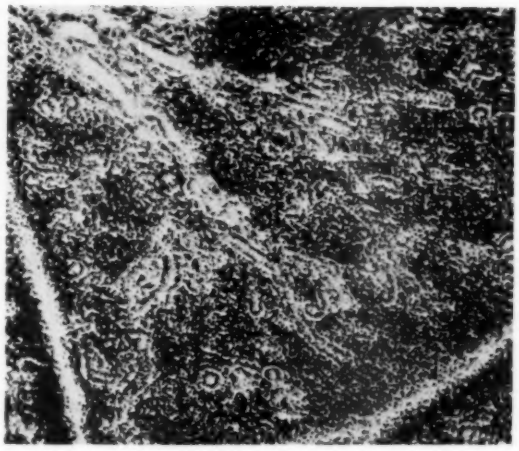


FIG. 2



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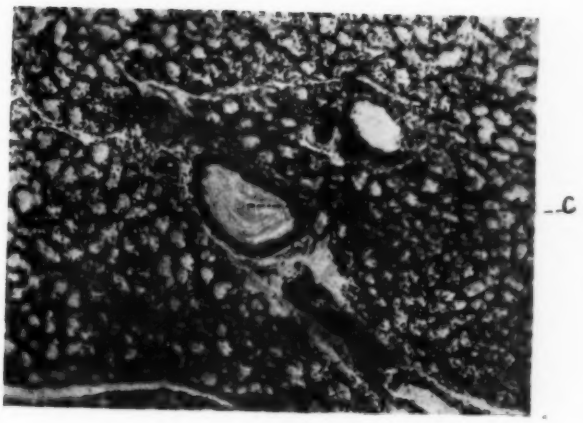

FIG. 4

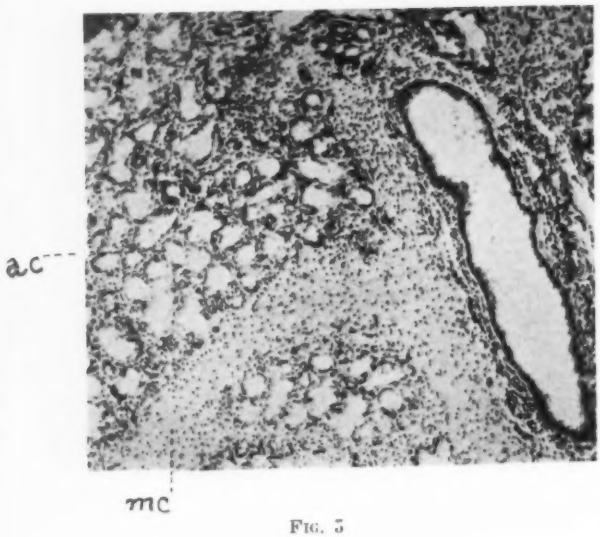

FIG. 5

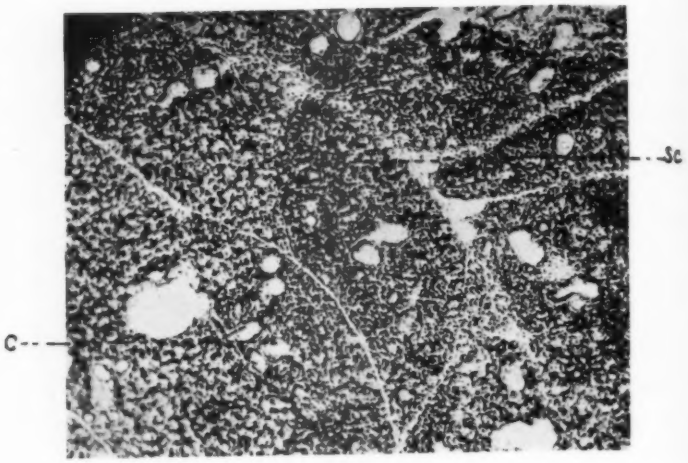

FIG. 6

FIG. 7

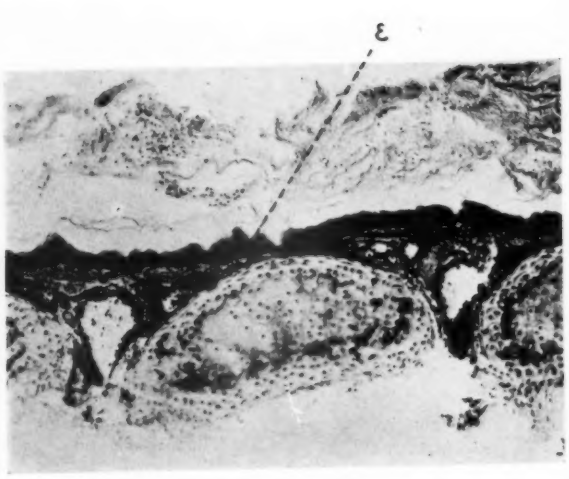

FIG. 8

because of the drying of the mucosa and loss of motility of the cilia of the epithelium. At any rate just as xerosis of the cornea is followed by secondary infection and the formation of corneal ulcers, so xerosis of the larynx and trachea is followed by inflammatory changes which eventually spread and involve the bronchi in the lungs.

The secretion of tears is, as a rule, either scanty or absent in children suffering from xerophthalmia or keratomalacia even during crying. These children are, as a rule, very hoarse and the voice is never clear. As is the case in rats with experimental xerophthalmia, the larynx in children is implicated in the pathological process, and like the rats the children usually die from bronchopneumonia. The pathological changes in rats explain the hoarse voice, the cough, bronchopneumonia and bronchitis, and the absence of tears and saliva which are seen in human cases of this disease.

If two per cent of cod-liver oil be added to the diet of xerophthalmic rats, the conjunctival sac becomes moistened, the number of bacteria becomes diminished, the xerotic change in the epithelium disappears. Coincidently with the healing of the xerosis of the eye the lacrimal and salivary glands become normal histologically and they show histological evidence of secretion.

The results of these studies make it seem probable that the effect of cod-liver oil, or fat-soluble A, is not exerted directly upon the tissues of the eyes and the lids. More probably the vitamin acts, either directly or indirectly, on certain of the secreting glands in the body to insure their normal function, which is held in abeyance if the animal is deprived of his optimal intake of the vitamin. From this point of view it is necessary to consider the clinical picture of xerophthalmia as a series of secondary symptoms which are indicative of hypo-function of a certain part of the secretory apparatus of the organism. In other words, xerophthalmia, as it is ordinarily seen, is the manifestation of a specific glandular lesion. It is one of a chain of symptoms, the other links of which are hoarseness, cough, lack of saliva, sterility, and general malnutrition.

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DESCRIPTION OF FIGURES

FIG. 1.—Shows the shrinkage of the cells of the lacrimal gland (L) and the Harderian gland (H).

FIG. 2.—The retention cyst formed as the result of the occlusion of the duct of the Meibomian gland (M) of lid.

FIG. 3.—To show the shrinkage of the secreting cells of the submaxillary gland.

FIG. 4.—This figure shows the cornification (C) of the epithelium of the principal duct of the sublingual gland.

FIG. 5.—Atrophy of the sublingual gland cells and extrusion of mucus into the interstitial connective tissue caused by the occlusion of the principal duct.

FIG. 6.—Cornification (C) of the intra-lobular ducts of the parotid gland and the partial shrinkage of the secreting cells (SC).

FIG. 7.—Infection through the duct of the submaxillary gland (I). The epithelium of the duct is very much thickened and the glandular cells have become atrophic (C).

FIG. 8.—This figure shows xerosis of the epithelium of the trachea and the desquamation of the cornified and thickened epithelium (E).

NOTE ON A MODIFICATION OF THE CHROMAFFIN REACTION, WITH OBSERVATIONS ON THE OCCURRENCE OF ABDOMINAL CHROMAFFIN BODIES IN MAMMALS

By G. B. WISLOCKI

(From the Anatomical Laboratory of The Johns Hopkins University)

That the cells of the medulla of the adrenal glands give a brownish reaction when fixed in a solution containing a salt of chromic acid was first observed by Henle ('65). This observation was extended by Stilling ('90), who showed that in the dog, cat, and rabbit there are groups of cells associated with the sympathetic nervous system, that react similarly with chromium salts. These he called "chromophil cells." Kohn ('03) abundantly confirmed Stilling's observations, showing, in the cat and rabbit particularly, that "chromaffin cells," as he designated them, occur frequently in association with the sympathetic nervous system, either as microscopic clusters of cells embedded in the ganglia, or as bodies of macroscopic size located in the sympathetic plexuses. These groups of cells he termed "paraganglia." He directed attention to a conspicuous strip of chromaffin cells situated ventral to the abdominal aorta and superior to the inferior mesenteric artery, which was present in all of the mammals he studied and which he termed the "paraganglion aorticum abdominale." Finally, Zuckerkandl ('01) discovered a group of paired bodies in the region of the inferior mesenteric artery in human fetuses and new-borns which gave the chromophil reaction. These are usually referred to as the "organs of Zuckerkandl."

The methods employed by all subsequent observers for demonstrating these bodies have been those recommended by Stilling and Kohn. The retroperitoneal tissue of the animal is exposed and cotton, saturated with 3.5 per cent potassium bichromate, is placed in the abdomen for from 6 to 12 hours. The reproperitoneal tissue is then excised and washed for several hours in running water and then examined for the presence of chromaffin bodies, which, when present, should stand out as brownish strands or patches against a lighter colored background. A modification of this method consists in immediately excising the tissue suspected of containing chromaffin bodies and immersing it in 3.5 per cent potassium bichromate for the same length of time, followed by washing. It is advisable to transfer the tissue finally to glycerine in order still further to bring out the chromaffin bodies.

When subsequent microscopical examination of the tissue is desired, it is recommended that the chromaffin reaction be performed by fixation in formalin-bichromate (formaldehyde 40 per cent, 10 c.c.; potassium bichromate, 3.5 per cent, 90 c.c.). In all of these methods it is of course desirable that the tissue be fixed as soon after death as possible, for in the course of 6 to 18 hours post mortem the reaction no longer occurs in the chromaffin cells.

That the technique is sufficient to demonstrate the chromaffin bodies in man, dog, cat and rabbit is evidenced by the observations of Stilling, Kohn and Zuckerkandl and the subsequent ones of Swale Vincent ('12) and Kahn ('12). Although the principal bodies are readily distinguishable to the naked eye, in these animals, small scattered bits of chromaffin tissue cannot always be differentiated from clotted or extravasated blood without microscopic examination. Furthermore, Swale Vincent ('12) has been unable to discover any chromophil bodies in some animals, viz., monkey, pig, guinea-pig, rat, gopher, and squirrel. Kahn ('12) also reports the absence of macroscopic chromaffin bodies in four adult monkeys examined by him. One might assume that all of these animals lack macroscopically demonstrable chromaffin bodies. On the other hand, a suspicion might be aroused that the chromaffin reaction, as at present performed, is inadequate for their demonstration. The author proposed therefore to modify the technique, as heretofore used, and to investigate a number of animals for the presence or absence of chromaffin bodies. In the present paper this modified technique is described, together with results obtained in the few mammals which it was possible to secure for this purpose.

Technique

The tissue to be studied was excised from the freshly killed animal, washed as free of blood as possible in running tap-water and placed in a large volume of fixative consisting of 90 parts of 3.5 per cent potassium bichromate and 1 part of 40 per cent formaldehyde (Kohn's fluid). The tissue was not allowed to remain in this fixative over 3 hours, at the end of which time the chromaffin reaction was complete; it was then rinsed in tap-water and transferred for further fixation to 10 per cent formalin for 24 hours, after which it was washed thoroughly in running water and transferred successively to 60 and 70 per cent alcohol. The tissue was bleached by allowing it to stand for from 6 to 24 hours in sunlight in several changes of 70 per cent alcohol, prepared by adding 20 parts of hydrogen peroxide U. S. P. and 10 parts of water to 70 parts of alcohol. When completely bleached, the tissues, other than the chromaffin bodies, appear perfectly white. The chromaffin bodies stand out conspicuously (depending on the species of animal), as lemon-yellow to dark brown bands, threads, dots, or patches against a white background. The material may now be stored in 80 per cent alcohol, or portions of it embedded and cut. Excellent permanent gross preparations were obtained by dehydrating the material and clearing it in benzol and methyl salicylate according to the Spalteholz method. In these transparent preparations the chromaffin tissue stands out as a series of brown bodies whose position in reference to the blood-vessels is readily visible.

The observations of the earlier investigators concerning the size, shape, number, color, and distribution of the abdominal chromaffin bodies in the dog, cat, rabbit and in man have been amply confirmed by this technique. Further, the opossum, guinea-pig, squirrel, rat, and monkey were examined and, with the exception of the rat, abdominal chromaffin tissue was demonstrated macroscopically in all of them.

Opossum (two adult females).—On bleaching the retroperitoneal tissues, from 8 to 10 lemon-yellow bodies, about 1 mm. in diameter, became visible, scattered irregularly in a plexus of nerves extending from the level of the adrenal glands to the bifurcation of the aorta. On section these bodies proved to be ganglia in which were embedded groups of from 10 to 30 cells whose cytoplasm contained dark brown stained material (Fig. 1).

Guinea-pig (three adult males and three adult females).—In every instance, on examining the bleached retroperitoneal tissue, a conspicuous orange-colored stellate mass, measuring 2 mm. in diameter, was observed in the midline in the cœliac plexus, immediately below the superior mesenteric artery. On section this proved to be a mass of cells possessing a distinct capsule and exhibiting a characteristic chromaffin reaction (Fig. 2). No chromaffin bodies were demonstrable in the gross elsewhere in the abdomen.

Squirrel (one adult male grey squirrel).—After bleaching, an orange-colored mass, measuring 2 mm. in diameter and irregularly stellate in outline, became visible in the midline in the cœliac plexus immediately below the superior mesenteric artery. On section this proved to be

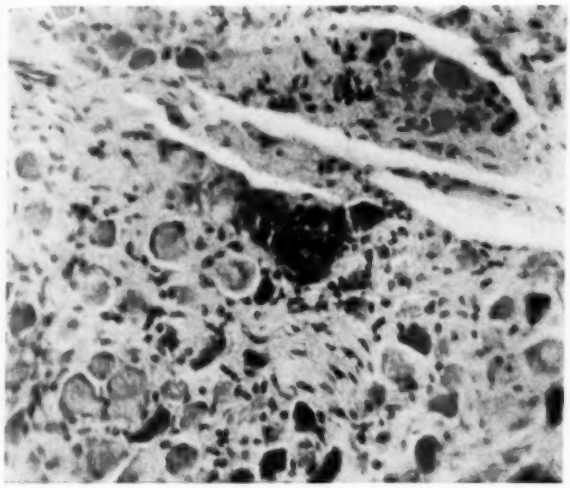

FIG. 1

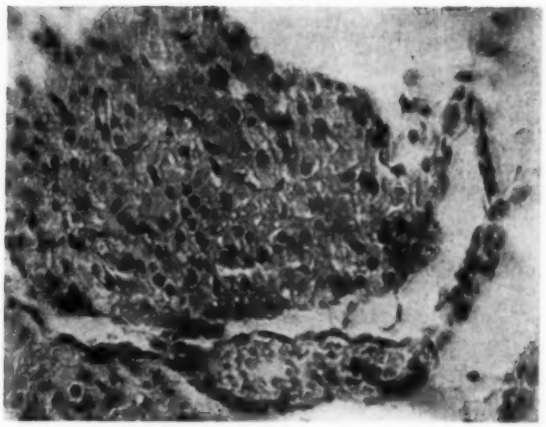

FIG. 2

FIG. 3

FIG. 4

Plate.—Wislocki, G. B. A Modification of the Chromaffin Reaction, with Observation on the Occurrence of Abdominal Chromaffin Bodies in Mammals.

a characteristic group of chromaffin cells (Fig. 3). No chromaffin tissue was visible to the unaided eye elsewhere in the abdomen.

Rat (three adult males and three adult females).—After bleaching the retroperitoneal tissue, the material was carefully examined with the naked eye and with the aid of a lense, but no masses of chromaffin tissue could be discovered.

Monkey (one adult female macaque).—After bleaching the retroperitoneal tissue, a series of small yellow bodies appeared, extending in a broken chain from the region of the superior to the inferior mesenteric arteries. The largest of these measured 2 mm. in length. On section these bodies proved to be typical masses of chromaffin cells (Fig. 4).

SUMMARY

A modification of the technique for demonstrating chromaffin tissue is described, whereby the presence of chromaffin bodies of macroscopic size can be demonstrated in the retroperitoneal tissue of the opossum, squirrel, guinea-pig, and monkey.

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DESCRIPTION OF PLATE

Fig. 1. Sympathetic ganglia from the aortic plexus of an opossum, showing a group of chromaffin cells. (× 400.)

Fig. 2. Chromaffin body from the coeliac plexus of a guinea-pig. (× 320.)

Fig. 3. Chromaffin body from the cœliac plexus of a squirrel. (× 290.)

Fig. 4. Chromaffin body from the aortic plexus of a macaque. (× 200.)

ON THE CARDIAC COMPLICATIONS OF GONORRHOEA

By W. S. THAYER, M. D.

(*Baltimore*)

The old concept of gonorrhœa as of a local process in which complications arise largely through direct extension, or as a result of secondary infections, has long since been abandoned. The chills, prostration, leucocytosis, anæmia, which are associated with the common complications of gonorrhœa, epididymitis, cystitis, pyelitis, synovitis, arthritis, the fever and more or less severe general symptoms which may attend the onset of an apparently uncomplicated specific urethritis, are often, in their severity, quite out of proportion to the apparent gravity of the focal process. They are indeed manifestations which might lead us to suspect the existence of a septicæmia. And since the communication of Hewes in 1894, from various sources there has been accumulated abundant evidence that gonococci are often present not only in the focal lesions but also in the circulating blood. Furthermore, it has been shown that 'tis not only in those cases with grave general manifestations that septicæmia may be demonstrated. Gonococci have been found in the circulation in instances of mild continued fever in apparently uncomplicated gonorrhœa (Thayer, 1905).

The occurrence of endocarditis as a complication of gonorrhœa and its direct dependence on the diplococcus of Neisser has now been demonstrated by many observers.

Gonorrhœa, then, is an infection, focal at first, which spreads not only by direct extension, but also and not infrequently, through the blood stream—a general septicæmia associated with a variety of metastases, notably arthritis, synovitis, myositis and not infrequently endomyo- or peri-carditis.

How frequently and under what guise do we meet with the cardiac complications of gonorrhœa?

This is a very difficult question to answer, and consultation with the literature leaves one often in doubt because of the insufficiency of the criteria on which diagnoses are made. The one source of accurate information, at the outset, is the study of those fatal cases which have been confirmed by necropsy.

There is a considerable literature dating from the sixties and before, concerning gonorrhœal peri- and endocarditis. At the outset these complications were generally regarded as secondary infections. Gradually, since the discovery of the gonococcus, and especially, since 1889, evidence has been accumulated which has demonstrated that these complications are in the beginning generally pure gonorrhœal infections.

The consecutive steps by which this conclusion was reached were:

1. The demonstration of gonococci, microscopically in the focal lesions at necropsy.

2. The association of this observation with the negative results of cultures taken *intra vitam* on ordinary media.
3. The obtaining of positive cultures, *intra vitam*, and the demonstration of the organisms, microscopically and by culture, in the blood or valvular vegetations at the necropsy.
4. Reproduction of an acute urethritis in man by inoculation with gonococci obtained at the necropsy from the affected valves.

In 1899, the writer had already collected thirty-two instances of well-described ulcerative and vegetative endocarditis associated with gonococcal infection, with post-mortem records, and fifteen in which the purely gonococcal nature of the infection might fairly be accepted.

The occurrence in the medical service of the Johns Hopkins Hospital, in the summer of 1920, of a case of gonorrhœal endocarditis of the pulmonary valves has turned our attention again to a subject in which we have been interested for years. Since then we have observed two additional cases. We have, accordingly, reconsidered our experience with gonorrhœal endocarditis at the Johns Hopkins Hospital during the last thirty-three years.

At the outset it may not be uninteresting to record briefly the three recent cases above referred to.

CASE I. *Gonorrhœa. Ulcerative and vegetative endocarditis of pulmonary valves—Cultures from the circulating blood, negative—Gonococci demonstrated in the valvular thrombi at necropsy and cultivated from the kidney.*

E. R., (Med., 44082; Path., 6319), a coloured boy of 19, between ten and eleven weeks before his death was seized with a stitch in his right side associated with a palpable friction rub. This was followed by fever, chills, sweats, cough, progressive weakness, increasing anæmia (R.b.c., 4,224,000; hb., 80%;—R.b.c., 2,528,000; hb., 28%), high leucocytosis (20,000-28,000). There was moderate cardiac enlargement with some dullness in the first and second left spaces, and a loud to and fro murmur in the pulmonary area, well transmitted throughout the chest; no essential change in the aortic sounds. Irregular, intermittent fever (99.4°-103.8°); albuminuria; pus and blood in the urinary sediment.

Gram-negative diplococci, morphologically gonococci, were demonstrated in the prostatic fluid. Cultures from the blood were repeatedly negative.

The patient failed rather rapidly. The transverse diameter of the heart increased in extent and a systolic murmur became audible in the tricuspid area. Severe diarrhœa set in with blood-stained stools. Eight days later, ten weeks after onset, the patient died.

The course of events seemed to be clear. Acute ulcerative endocarditis of the pulmonic valve; pulmonary embolism with infarction and pleurisy causing the first subjective symptoms; intermittent fever, chills, progressive anæmia, gonorrhœal prostatitis, cystitis, pyelitis, nephritis, terminal colitis, death.

The *necropsy* wholly supported our clinical diagnosis. The heart was not remarkably enlarged. The aortic, mitral and tricuspid valves showed no abnormalities. There was an extensive ulcerative endocarditis with large, irregular, nodular vegetations on the pulmonic valve which showed no evidence of a pre-existing stenosis. There were two infarctions in the right lung, one older, in the right lower lobe, and partially organized, associated with pleural adhesions which occupied a position in the right axilla corresponding to the area in which the patient had complained of pain at the outset; the other, fresher, in the lower lobe posteriorly. There was acute urethritis, hæmorrhagic cystitis, and pyelitis. The kidneys were large, swollen, cloudy and dotted with small hæmorrhages.

Smears from the thrombi on the valves showed numerous Gram-negative, biscuit-shaped diplococci. Cultures from the kidneys revealed gonococci; blood and vegetations, negative. There was no evidence of a pre-existing pulmonic stenosis or indeed of any pre-existing valvular disease.

CASE II. *Acute vegetative and ulcerative aortitis with aneurysm formation—Cultures from circulating blood negative—Gonococci demonstrated in the focal lesions at necropsy.*

A. S. (Med., 45333; Path., 6545), a coloured man of 28, with an indefinite history of an attack, five years previously, of pain about his heart followed by occasional sensations of palpitation on exertion, was seized, 8 weeks before death, with an arthritis in the right ankle and shoulder, and transient pains in the other joints. The symptoms of arthritis soon disappeared but a cough set in, so distressing as to interfere with sleep. The sputa were scanty, but on the 21st of March, three and a half weeks before death, were blood-stained. There was progressive weakness, sweating at night, and five weeks after the onset of his illness, the severity of the symptoms brought the patient to the hospital.

On entrance there was orthopnœa and severe paroxysms of coughing. There was fever. The heart was enlarged and showed obvious evidence of aortic stenosis and mitral insufficiency with failure of the right side—enlarged, pulsating liver, œdema of the extremities. There was grave anæmia (R.b.c., 2,832,000; hb., 47%) and a high leucocytosis (13,000-22,240). There was moderate albuminuria, and on several occasions blood in the urinary sediment. Irregular remittent and intermittent fever continued, 99° to 102.6°; persistent cough. Petechiæ appeared in the conjunctivæ. Death followed a sudden paroxysm of coughing, eight weeks after the onset of his illness.

Cultures from the blood during life were repeatedly negative.

The symptoms were regarded as indicating an ulcerative endocarditis of the aortic valve. The history suggesting pulmonary embolism (bloody expectoration) pointed to the possibility of involvement of the valves of the right side or thrombi probably in the right auricular appendage. The slow course of the case, eight weeks' duration, was suggestive of an infection with attenuated streptococci or gonococci, and the negative results of cultures supported the possibility of its being gonorrhœal.

At *necropsy*, not obtained, unfortunately, until five days after death, there was found old chronic, fibrous aortic and mitral stenosis without acute changes. Somewhat above the aortic valves, however, as shown in the photograph, there was an acute ulceration of the aorta leading to an aneurysmal sac from which there were accessory dilatations. Around the edges of the sac and at its base were vegetations. The aortic wall had been torn through, and from the sac there exuded a thick gray fluid showing Gram-negative diplococci and a few Gram-positive cocci. Elsewhere the wall of the aorta was normal. Owing to the condition of the specimens, no cultures were made.

The overwhelming prevalence in the smears of organisms presenting the morphological and tinctorial characteristics of gonococci, when taken in connection with the negative blood cultures *intra vitam*, led us to regard the process as gonorrhœal. There were no other evidences of acute gonorrhœa.

CASE III. *Vegetative and ulcerative endocarditis of aortic valves—Cultures from circulating blood, negative—Gonococci obtained in pure culture from the valvular lesions at necropsy.*

M.M., (Med., 45977; Path., 6681), a healthy married woman of 21 was seized ten weeks before death, with arthritis in knees,

CASE II. A. S. Gonococcal endaortitis with the formation of an aneurysm.

ankles and hip, associated with irregular remittent and intermittent fever. The arthritis which was apparently at no time very acute, disappeared in 10 days, but the fever continued. Signs of aortic insufficiency set in with very collapsing pulse but without marked cardiac enlargment. There was pronounced dyspnœa. The patient became anæmic, was dull and confused mentally, and was brought to the hospital three weeks after the onset of her illness. In the hospital there was irregular intermittent and remittent fever (98°-103.5°); progressively increasing anæmia (R.b.c., 4,236,000 to 2,464,000; hb., 58% to 28%), and a marked leucocytosis (13,520 to 39,080). There were no petechiæ and no obvious embolic phenomena. The pulse increased steadily in rate. Striking and rapid changes occurred in the heart sounds and in the character of the pulse which was at first very collapsing, later much less so, while the intensity of the diastolic murmur diminished and the first heart sound became strangely accentuated at the base.

Persistent delirium; fever; tachycardia. Progressive failure. Evidence of chronic passive congestion (enlarged liver). Blood cultures, repeatedly negative. Death ten weeks after onset.

At first it was thought that the case might be an instance of acute rheumatic endocarditis, but the remarkably sudden onset of an aortic insufficiency of so high a degree and the relatively small heart—for, in the young, hypertrophy soon follows an aortic insufficiency of any extent, suggested an ulcerative endocarditis. This was borne out by the subsequent course of the case—the remittent, high fever, the progressive anæmia, the high leucocytosis and especially the sudden changes in the character of the heart sounds.

As we put together the facts, we could not help being impressed by the possibility that this might have been an instance of gonorrhœal endocarditis. In several similar cases in which cultures *intra vitam* were persistently negative, this has proved to be the case.

Necropsy showed an extensive vegetative and ulcerative endocarditis of the aortic valves, with large, white, crumbling vegetations, perforations of the valves, and an abscess extending from the valvular lesions into the muscle of the left ventricle. There was no evidence of pre-existing valvular disease, one curtain remaining delicate and unaffected. There were fresh splenic infarcts and small hæmorrhages into the pulp. The kidneys were large. There were old adhesions between the omentum and tubes and round ligaments, and thrombi in the pampiniform plexus. Gram-negative intracellular diplococci were demonstrated in smears, and pure cultures of gonococci were obtained from the focal lesions on the valves.

Since the opening of the Johns Hopkins Hospital, nearly thirty-three years ago, there have come to necropsy 327 instances of acute endocarditis. In 133 cases the nature of the process was determined bacteriologically,* either before death by blood cultures, or at necropsy. To these may be added 16 fatal cases in which necropsy was not obtained, although the nature of the process was determined by cultures from the blood *intra vitam*, as well as 27 cases with positive blood cultures in which the patients were removed from the hospital unimproved, making 176 altogether.

Twenty, or 11.3% of these instances, were due to gonococcus.

* There were others in which a bacteriological study was made, but the records and reports were destroyed in a recent fire in the Pathological Laboratory.

In 4 of these 20 cases, there were terminal infections; in 2 with streptococcus; in one with streptococcus and staphylococcus, and in one with pneumococcus. In all, gonococcus was evidently the primary cause.

Of these twenty cases, gonococci were cultivated *intra vitam* (10) or at necropsy in 14 instances.

Gonococci were demonstrated bacterioscopically at necropsy following negative cultures *intra vitam* or *post mortem* in 6.

There were two further cases which, clinically and anatomically, seemed to be gonorrhœal, with negative cultures *intra vitam* in which, owing to a misunderstanding, no bacteriological examination was made at death. These we have included in some of our tables.

In addition, there were several other cases in which the endocarditis may well have been gonorrhœal, although definite proof was wanting. One was a characteristic instance of ulcerative endocarditis appearing in the course of an acute gonorrhœa with negative blood cultures during life. No necropsy was allowed. These cases have not been used in the tables, although in the last instance the course of the illness, the negative blood cultures, and the sequence on gonorrhœa, render the diagnosis of gonorrhœal endocarditis highly probable. The summary of this case may be found in the appendix.

This is a rather large material for one clinic, dependent, probably, on the circumstance that we have been on the lookout for the condition.

Age: Of these patients the age varied from 9 to 42.

Sex: There were 16 males; 6 females.

Colour: Eleven were white, eleven were negroes—a large proportion of negroes, larger than was observed in other forms of endocarditis excepting pneumococcus infections.

Time of onset in relation to the gonorrhœa: But little evidence could be obtained as to the relation of the onset of the symptoms to the stage of the initial local infection. Among our twenty-two cases the cardiac complications appeared almost with the onset of the gonorrhœa in one instance. In four they appeared about two weeks after the onset; in two more within a month; in the others (fifteen) the relation to the time of onset of the gonorrhœa was uncertain. In several instances all traces of the urethritis had disappeared.

Relation of the onset of cardiac involvement to the other complications of gonorrhœa: In like manner little information was thrown on the relation of cardiac involvement to the occurrence of other complications of gonorrhœa.

Of our twenty-two cases but seven or 31.1% had had *arthritis* in the course of the illness. This is in sharp contrast to the figures in cases reported by other authors. Among 54 instances of proven gonorrhœal endocarditis collected from the literature in which there were notes as to the presence or absence of involvement of the joints, arthritis was noted in 37, or 68.5%. It is not impossible that this variance depends on the circumstance that where

routine bacteriological examinations are not made, the disease, in the absence of obvious urethral discharge or arthritis, is often overlooked.

Symptoms: The symptoms were uniformly those of a grave septicæmia. The onset was sometimes gradual, beginning with headache, lassitude, pains in the loins, or more sudden and initiated by a sharp chill. There was continued or irregularly remittent or intermittent fever, often associated with violent chills and sweating. *Chills* were present in the majority (63.6%) of our cases.

Blood: There was, as a rule, a rapidly developing anæmia. The red corpuscles ranged from 5,467,000 to 1,248,000 per c.mm.; the hb. from 92 to 17%. The longer the duration of the case, the more marked, as a rule, was the anæmia.

In all cases there was a well-marked leucocytosis. In but two instances were figures below 13,000 recorded and in each instance there was a leucocytosis later.

The leucocytes were over 15,000 in 19 of 22 cases.
The leucocytes were over 20,000 in 14 of 22 cases.
The leucocytes were over 30,000 in 7 of 22 cases.
The leucocytes were over 40,000 in 4 of 22 cases.

In one instance with a terminal pneumococcus pneumonia and septicæmia the leucocytes rose to 78,000 and 100,000.

Embolic phenomena were common, occurring in two-thirds of the cases—in skin, kidney, spleen, lungs, brain, heart muscle, skeletal muscles.

Symptoms of these embolic phenomena were not uncommon during life. *Pulmonary infarction,* for instance, gave rise to the initial symptoms in the first of the three cases described at the beginning of this communication. *Renal infarction* may be suspected by the transient presence of blood in the urine. Blood corpuscles were found in the urine of 10 of our cases. But occasional blood corpuscles are not uncommon in the nephritis so frequently present. Pain and tenderness in the left hypochondrium may reveal *splenic infarction.* In two of our cases there was a partial *hemiplegia.*

Cutaneous hæmorrhages, usually in the form of petechiæ on limbs or trunk or neck or mucous membranes of the mouth or conjunctivæ, were frequent. These were recorded in 6 of our 11 white patients—in but one of the negroes. Had the conjunctivæ and mucous membranes been examined with greater regularity 'tis probable that these figures would have been different.

An *acute* or *subacute nephritis* was present in the majority of our cases. This was manifested clinically by the presence of a considerable albuminuria with casts, leucocytes, epithelial cells and often blood in the urinary sediment. In 4 cases of long duration there was anasarca and hydrops. In general, the renal manifestations were more striking in the cases of longer duration.

The duration of our gonorrhœal endocarditis varied from 3-4 weeks to 8 months, averaging 9.7 weeks. If one subtract four cases in which there was a terminal mixed infection, the average duration was 10.5 weeks. In the majority of instances the course of the disease was from 4 to 9 weeks. The shortest case, the duration of which was not over 4 weeks, was that of a little girl with gonorrhœal peritonitis in which death was not the result of the endocarditis. In many of our cases, the picture was that of subacute vegetative endocarditis similar to that seen in infection with streptococcus viridans.

A comparison of these figures with those of endocarditis of other origin is not uninteresting.

TABLE I

Duration of fatal cases of acute bacterial endocarditis.

	Pneumococcus 4 d.-6 m. Av. 4.3 w.	St. aureus 3 d.-6 m. Av. 4.5 w.	St. albus 3-11 w. Av. 6.8 w.	Gonococcus 3 w.-8 m. Av. 10.5 w.	Strep. all strains few d.-9 m Av. 12.2 w.	Strep. vir. 3 w.-1 y. Av. 23.1 w.	Infucem 11-26 w. Av. over 6 m.
Under 13 weeks	21/22	20/24	4/4	18/22	37/60	4/22	1/3
" 9 "	20/22	20/24	2/4	16/22	34/60	3/22	—
" 6 "	17/22	20/24	2/4	8/22	31/60	3/22	—
" 3 "	11/22	14/24	0/4	1/22	20/60	0/22	—
" 1 week	4/22	5/24	—	—	10/60	—	—

Pneumococcus, in our experience, produces an acute infection, one half of our cases pursuing their course in less than 3 weeks. In but one of 22 cases was the duration above nine and a half weeks.

Staphylococcus aureus is not infrequently a terminal invader and in over half of our cases the process was rapidly fatal with a duration of less than three weeks. The duration was under 6 weeks in 83% of our cases. But while staphylococcus aureus endocarditis appears generally to be more acute and virulent than gonococcal, yet in 4 of our 24 cases the course was subacute, lasting from 13 weeks to 6 months.

There were four instances of pure staphylococcus albus endocarditis, the duration of which varied from 3 to 11 weeks, the average course being somewhat more chronic than in aureus infections.

In our group of streptococcus infections, because of the circumstance that our records go back through so long a series of years, during most of which no differentiation of type was made, all strains of the organism are included. It is not therefore surprising to find a great variation in the duration of the disease. Thus 20 of 60 cases were peracute, of under 3 weeks' duration, 11 of these running their course in a week or less. On the other hand 23 of the cases or over one-third lasted 13 weeks or over. Of these, all were probably instances of infection with streptococcus viridans.

In 22 cases in which S. viridans was identified bacteriologically, the duration ranged from 3 weeks to a year, averaging 23.1 weeks. In only 3 instances in which streptococcus viridans was isolated was the duration under 13 weeks, and in one of these instances it was a

terminal infection in pernicious anæmia. It would appear that hæmolytic streptococci are associated generally with rapidly fatal infections.

There were three fatal cases of endocarditis due to organisms of the B. influenzæ group. These were all chronic, lasting from 11 to 53 weeks.

Gonococcus seems to give rise to an endocarditis of a malignancy between that depending on staphylococcus and pneumococcus on the one hand and the slower viridans and influenzal infections on the other. The rapidity of the course and malignancy of bacterial endocarditis rises, in our experience, in the following sequence:

1. B. influenzæ
2. Streptococcus viridans
3. Gonococcus
4. Staphylococcus albus
5. Staphylococcus aureus
6. Pneumococcus
7. Streptococcus hæmolyticus

Anatomical Lesions: The anatomical lesions were those of a vegetative and ulcerative endocarditis, sometimes spreading to the walls of the ventricles or upwards into the sinuses of Valsalva, associated often with extensive destruction of valves and aneurysm formation, sometimes infiltrating the adjacent muscle as suppurative myocarditis. In general, the vegetations formed large, rather brittle, yellowish gray masses.

The only instance in which the vegetations were not large was that of a girl of 9 who died of a general gonococcal infection with peritonitis. Here the lesions were on the wall of the aorta above the valves and were of short duration—not over four weeks—probably somewhat less. In one other instance—that of A. S., described at the beginning of this communication—the lesions were those of a vegetative and ulcerative aortitis.

The abundance and size of the vegetations were commonly in direct relation to the duration of the case.

Mural endocarditis: The vegetations extended onto the wall of the heart in 8 of 20 cases, involving the left ventricle, papillary muscles and chordæ tendineæ in 5 cases, the right side in 4, the left auricle in one.

Vegetative and ulcerative aortitis: Two of the twenty cases coming to necropsy showed a vegetative and ulcerative aortitis alone. In two other cases, in addition to the valvular lesions, there were vegetations on the aortic wall.

Acute pericarditis occurred in four of the cases.

In one case there was a peri-aortic suppuration in the loose connective tissue just above the valves. There was *pleurisy* in two cases, in one of which gonococcus was cultivated from the fibrino-purulent fluid.

Our figures, as might be expected, show that the left side of the heart is affected more often than the right, but the percentage of right-sided involvement is remarkably high, considerably higher than in those cases of gonorrhœal endocarditis that we have collected from other sources. This high proportion of affection of the right side was also found in staphylococcus endocarditis, and is in rather sharp contrast to that which is shown by the figures for pneumococcus and streptococcus. In general, however, it is in accord with the well-recognized relative frequency of acute ulcerative lesions of the right side of the heart.

TABLE II

Anatomical distribution of the lesions.

		Gonococcus			St. aureus 24 cases	St. albus 4 cases	Pneumococcus 25 cases	Streptococcus 52 cases
		J. H.H. series 20 cases	Literature 60 cases	Combined 80 cases				
Left side	A	6	30	36	6	2	9	9
	M	2	15	17	7	1	4	17
	AM	2	8	10	4	0	6	16
	Aorta, mural	2	0	2	0	0	0	0
		12-60%	53-88.3%	65-81.2%	17-70.8%	3-75%	19-76%	42-80.7%
Right side	P	4	1	5	1	0	1	1
	T	1	0	1	5	1	1	2
	PT	0	1	1	0	0	0	0
		5-25%	2-3.3%	7-8.7%	6-25%	1-25%	2-8%	3-5.7%
Both sides	AP	0	1	1	0	0	0	0
	AT	2	1	3	1	0	1	0
	MT	0	0	0	0	0	0	1
	APM	0	1	1	0	0	0	0
	APT	1	0	1	0	0	0	1
	AMT	0	1	1	0	0	3	3
	AMPT	0	1	1	0	0	0	2
		3-15%	5-8.3%	8-10%	1-4.1%	0	4-16%	7-13.4%

TABLE III

Distribution of the affection among the individual valves.

	Gonococcus		St. aureus 24 cases	St. albus 4 cases	Pneumo. 25 cases	Strep. 52 cases	S. viridans 13 cases
	J..H. H. series 20 cases	Total cases collected 80 cases					
A	13-65%*	56-70%	12-48%	2-50%	19-76%	32-61.5%	8-61.5%
M	4-20%	30-37.5%	11-44%	1-25%	13-52%	39-75%	11-84.6%
P	5-25%	10-12.5%	1-4%		1-4%	4-7.6%	1-7.6%
T	4-20%	8-10%	6-24%	1-25%	6-24%	9-17.3%	

* Including two instances of mural aortitis.

Of the individual valves the aortic was affected with greatest frequency; the pulmonary next, in a quarter of our cases. This is somewhat striking and again in contrast to the usually accepted figures which show a somewhat larger percentage of aortic involvement—70% in the combined 80 cases of reasonably proven gonococcal endocarditis that we have collected.

One striking point, however, that stands out in these figures is the greater frequency of the involvement of the mitral valve in streptococcal infections than in gonococcal, staphylococcal and pneumococcal endocarditis.

The probable explanation of this divergence is found when we consider:

(1) The relative frequency of pre-existing valvular disease so far as could be determined by the histories and the anatomical changes.

(2) The relative frequency with which previously unaffected valves were involved.

TABLE IV

Evidence of pre-existing valvular disease.

Gonococcus	Staph. aureus	Staph. albus	Pneumococcus	Streptococcus
4/20 or 20%	10/24 or 41.6%	1/4 or 25%	9/25 or 36%	35/52 or 67.3%

There was evidence of pre-existing valvular disease in only 20% of our gonorrhœal cases; in 41.6 of the staphylococcus aureus cases; in 25% of the four albus cases; in 36% of the pneumococcus infections as against 67.3% for our streptococcus cases. This is a striking contrast. 'Tis clear that acute streptococcus endocarditis was commoner in patients with chronic valvular disease, whereas the contrary was true in infections with the other organisms.

If, now, we consider, among the valves themselves, the relative frequency in which the affection was found on previously undiseased valves, it appears that the valves involved were, so far as could be determined, previously unaffected in the following percentages of the several commoner types of infection.

TABLE V

Per cent in which the acute process involved previously unaffected valves.

Gonococcus*	Staph. aureus	Staph. albus	Pneumococcus	Streptococcus
91.2%	65.5%	75%	65.7%	39.2%

* Not including the mural aortitis.

In other words, in more than half of our cases, 61%, Streptococcus attacked previously diseased valves—in sharp contrast to the behaviour of the other chief causal agents of acute endocarditis, notably of Gonococcus. *But the prevalence of mitral involvement in chronic endocarditis is well known.* If, as seems probable, Streptococcus attacks, generally, previously diseased valves, its predilection for the mitral valve may well depend largely on the circumstance that chronic mitral disease is very common.

Further light on this question might be obtained by a consideration of the relative percentage in which the individual valves are involved among those primarily affected.

TABLE VI

Relative percentage of involvement among those valves primarily affected.

	Gonococcus	Staph. aureus	Staph. albus	Pneumococcus	Streptococcus
A	10* 45.4%	4-21%	1-33.3%	13-52%	12-37.5%
M	4 18.1%	8-42.1%	1-33.3%	9-36%	14-43.7%
P	5 22.7%	1-5.2%		0-0	1-3.1%
T	3 13.6%	6-31.6%	1-33.3%	3-12%	5-15.6%

* Not including the two mural aortitides.

The figures would appear to show a tendency toward aortic involvement in gonococcal and pneumococcal infection, toward involvement of the mitral in infections with streptococcus and staph. aureus. But the number of cases on which the table is based is so small as to render it practically worthless.

In summary, then, the cardiac complications of gonorrhœa, as we have seen them, appear usually in the form of an acute or subacute vegetative and ulcerative endocarditis which comes on at varying periods in the course of the infection, often in the absence of other apparent complications. The onset may be sudden or more gradual, but is generally rather acute. There are usually chills and high remittent or intermittent fever, rapidly developing anæmia and considerable leucocytosis.

The constitutional symptoms, those common to all grave general infections, are usually early and profound. There is often a petechial eruption. Embolic phenomena of various sorts are common. There is albumin, casts, often blood in the urine, and, in the longer cases, anasarca and hydrops give evidence of a grave nephritis.

The duration is generally from 5 to 9 weeks, but longer subacute cases may occur.

The aortic valve is that most commonly involved but, as in all acute ulcerative endocarditides, the right side appears to be affected more often than in the chronic so-called rheumatic valvular disease. In our experience involvement of the pulmonary orifice has been rather common. Gonococcus usually involves healthy, previously unaffected valves. Mural endocarditis is common. Suppurative myocarditis, as described in 1893 by Councilman, may occur. Pericarditis is not infrequent.

Gonorrhœal endocarditis is generally a malignant process pursuing a progressive and fatal course. In its virulence it occupies a position between the slower and more subacute viridans and influenza infections and the more virulent albus, aureus, pneumococcus or s. hæmolyticus endocarditis.

But is gonorrhœal endocarditis always fatal? May recovery occur?

If so, what is its frequency and what is the prognosis?

Gonorrhœal septicæmia with every evidence of endocarditis is not necessarily fatal. Characteristic instances of acute endo- or peri-carditis have been recorded in which gonococci were cultivated from the blood during life with subsequent recovery. Good examples are the cases reported by Silvestrini, Withington, Dieulafoy, and Marfan and Debré.

Silvestrini records the case of a man, 29 years of age, who acquired gonorrhœa a month before entry into the hospital. He was treated with injections of wine—an unworthy abuse of a noble fluid. Eleven days after apparent recovery, anorexia, malaise, chills and sweats set in. On the third day there were pains in the joints of the

spine with swelling and redness of the accessible joints. The patient's appearance was typhoidal. In the subclavicular fossæ there appeared erythematous patches with central hæmorrhages. The cardiac impulse was in the fifth space in the mammillary line. There was an intense systolic murmur in the mitral area, and a doubled second sound. A pericardial friction rub was audible. The spleen was enlarged. There was a well-marked leucocytosis. Gonococci were cultivated from the blood, joints and urethral discharge. The pericardial friction disappeared and the patient gradually recovered.

The heart diminished in size but a harsh systolic murmur at the apex and a reduplicated second sound persisted. The patient left the hospital with ankylosis of several joints, and returned nine months after the onset of his trouble, still showing evidence of chronic mitral disease with systolic and presystolic murmurs.

Withington had the opportunity of observing a man of 26 who acquired gonorrhœa and, two weeks later, measles. Soon after convalescence from measles, præcordial pain set in, associated with chills, irregular fever and orthopnœa. There was cardiac enlargement, gallop rhythm and evidence of solidification at the bases of the lungs. There was a left femoral thrombo-phlebitis. A pericardial friction rub appeared and a short systolic murmur was heard in the fourth intercostal space to the left of the sternum. Cultures from the blood showed gonococcus.

Gradually the patient recovered, the temperature reaching normal about three weeks after the onset of the symptoms pointing to cardiac involvement. The heart returned almost to its normal size but a systolic murmur persisted in the second left space.

Dieulafoy reports the case of a man of 23 who was admitted to the hospital with headache, diarrhœa, high remittent fever and sweating. Two days later a mitral systolic murmur appeared, soon becoming loud and rough. There was an urethral discharge in which gonococci were present. Cultures from the blood, *intra vitam,* showed gonococci. The patient was very ill. There was bronchopneumonia. After treatment by rest and gonococcal vaccine, the patient gradually recovered and left the hospital well. The evidence of a mitral lesion remained.

Marfan and Debré report the case of a little girl, aged 10½, who, about a week before entry into the hospital on 24/VI, began to suffer from pain in the abdomen, fever and exhaustion. There was obvious pelvic peritonitis. The heart was somewhat enlarged with a slight systolic thrill and an intense, rough, systolic murmur transmitted outwards into the axilla. Five days after entry there was a pericardial friction murmur. High, irregular fever. Cultures from the circulating blood showed characteristic gonococci.

Treatment with gonococcic vaccine and anti-meningococcic serum. Gradual recovery after about 3 weeks, with persistent signs of mitral insufficiency and adherent pericardium. Ten months after the beginning of her illness the child still showed signs of adherent pericardium and mitral insufficiency.

Gourvich, in 1897, in an excellent study of the literature which has passed almost unnoticed, brought together a considerable number of instances in which transitory cardiac manifestations, interpreted as endocarditis, had been observed in the course of gonorrhœa. Many of these are suggestive but most consist of the description of systolic murmurs at the apex of the heart appearing during the height of the process and disappearing with recovery. Similar cases have been reported by other observers since the article of Gourvich.

The recognition of mild, early endocarditis is often very difficult, indeed impossible. Systolic murmurs at the apex and pulmonary areas are commonly heard in the course of any acute infection, and, in themselves, offer little basis for the diagnosis of endocarditis. In many instances of rheumatic fever 'tis only through long continued observation of the patient that a positive diagnosis of endocarditis is reached, and then only on the strength of the later mechanical effects of scarring and retraction of the valves in the production of permanent stenoses and insufficiencies.

The very frequency of gonorrhœa contributes to the difficulty of ascertaining its relation to endocarditis. Few genito-urinary surgeons, probably, examine the hearts of their patients as a routine procedure, and without knowledge of the condition of the heart at the time of onset of the gonorrhœa, it may be difficult or impossible to reach a conclusion as to the relation of the malady to a chronic valvular disease which is recognized later.

Our impression, and it must be acknowledged that it is but an *impression,* is, that the analogy between the cardiac complications of gonorrhœa and those occurring in pneumococcus and staphylococcus infections is close; that while mild infections with a favorable course may occur, gonorrhœal endocarditis is generally a serious affair, in no way comparable to the acute, verrucous, so-called rheumatic endocarditis of uncertain origin, which affects so commonly the mitral valves, and tends toward recovery with scarring, deformity, and the production of chronic lesions which are notoriously a seat of predilection for later streptococcal invasion with the development of acute and subacute vegetative and ulcerative lesions.

How often endocarditis occurs in gonorrhœa we have no clear idea. This, however, we do know. Gonorrhœal endocarditis is not a very infrequent malady, forming upwards of 11% of our fatal acute endocarditides, the bacterial nature of which has been determined at necropsy.

Summary and Conclusions

The cardiac complications of gonorrhœa occurring in thirty-three years at the Johns Hopkins Hospital have been reviewed. Twelve hitherto unreported cases have

been added to our series * and considered in connection with sixty cases collected from the literature.

In 176 instances of acute endocarditis of determined origin 20, 11.3%, were gonococcal.

Gonococci were cultivated *intra vitam* (10) or *post mortem* in 14 instances; they were demonstrated bacterioscopically following negative cultures *intra vitam* or *post mortem* in 6 instances.

There were two additional cases, in all probability gonorrhœal, with negative cultures during life in which no bacteriological examination was made at necropsy, and several other instances of more or less characteristic endocarditis occurring in the course of acute gonorrhœa with negative blood cultures but without necropsy; these latter cases were not considered in our tables.

But little evidence could be obtained as to the relation of the time of onset of the cardiac involvement to the appearance of the disease or other complications. Arthritis occurred in but 41.1% of our cases but in 68.5% of 54 cases collected from other sources.

The cardiac complications of gonorrhœa, as we have seen them, appear usually in the form of an acute or subacute vegetative and ulcerative endocarditis which comes on at varying periods in the course of the infection, often in the absence of other apparent complications. The onset may be sudden or more gradual, but is generally rather acute. There are usually chills and high remittent or intermittent fever, rapidly developing anæmia and considerable leucocytosis. The constitutional symptoms, those common to all grave general infections, are usually early and profound. There is often a petechial eruption. Embolic phenomena are common. There is albumin, casts, often blood in the urine, and in longer cases, anasarca and hydrops give evidence of a grave nephritis.

The duration is usually from 4-9 weeks but longer subacute cases may occur.

The aortic valves are those most commonly involved but, as in all acute endocarditides, the right side appears to be affected more often than in the chronic, so-called rheumatic valvular disease. In our experience, involvement of the pulmonary orifice has been rather common. Gonococcus usually implicates healthy, previously undiseased valves. Mural endocarditis is frequent.

The cardiac involvement is not restricted to the endocardium. Endaortitis, pericarditis and suppurative myocarditis are not unusual.

Gonorrhœal endocarditis is in general, a malignant process pursuing a progressive and fatal course. In its virulence it occupies a position between the slower and more subacute *S. viridans* and *B. influenzæ* infections and the more virulent *Staph. albus, Staph. aureus, Pneumococcus* or *S. hæmolyticus* endocarditides.

Milder instances of gonorrhœal endocarditis or pericarditis with recovery may occur. How frequent these are is not clear. It is our impression that they are relatively rare.

Gonorrhœal cardiac infections as a whole are by no means very unusual.

* See appendix.

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The table of references is arranged in alphabetical order. Beside the references to the authors mentioned in the text there are included references to the articles describing the eighty cases of gonorrhœal endocarditis from which some of the tables have been made.

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APPENDIX

Ten of our twenty-two cases of gonorrhœal endocarditis have already been reported by Thayer and Blumer, Thayer and Lazear, Harris and Dabney, Harris and Johnston and Thayer. In addition to the three cases reported in the body of the article there remain nine which are here given in summary. An additional tenth case with negative cultures during life which did not come to necropsy is also summarized because of its characteristic course.

CASE IV. *Pregnancy—Ulcerative endocarditis of mitral (?) valve. Pericarditis. Gonococci obtained in pure culture from circulating blood. Obstinate vomiting. Abortion. Death. Necropsy refused.*

A. B., (Med., 18490; 18505.) A healthy woman of 39 who had had nine children, began, on the first week of May 1905, to suffer with stiffness of the legs and arms and, 4 days later, with pain, tenderness and swelling of the dorsum of the right hand. Several days later, chills, fever and severe headache set in, recurring daily and associated with vomiting and soreness in the epigastrium. She was about 6 months pregnant. She entered the hospital something over three weeks after the onset of the illness. There was anæmia (R.b.c., 3,700,000-2,007,000; hb., 65%-42%). Moderate leucocytosis (10,800-16,800). The urine showed a trace of albumin and many leucocytes and hyaline and granular casts. Heart, enlarged; loud systolic murmur at the apex, transmitted into the axilla and the back; second sound accentuated in the pulmonary area.

The patient remained in the hospital for the greater part of the next 5 weeks. There was high intermittent fever with chills. The leucocytes rose at one time to 31,000. The anæmia was progressive. Petechiæ appeared on the trunk. Jaundice set in. Delirium. Progressive enlargement of the liver which, on the 15th of June, was 8 cm. below the costal margin in the mammillary line. The patient aborted on the 17th of June without change in her symptoms. Obstinate vomiting. Friction rub over the præcordium. On the 18th of June, about 6 weeks after the onset of symptoms, she died.

Vaginal smears were negative for gonococci. After two negative blood cultures, on 12 June, 12 cc. of blood which clotted in the syringe was expelled into a flask of bouillon and a flask of milk. In both flasks there appeared, in the clot, colonies which proved to be characteristic gonococci; these were transferred successfully to hydrocele fluid agar and human blood serum. Necropsy refused.

CASE V. *Gonorrhœa. Arthritis. Ulcerative aortic endocarditis. Gonococci obtained in pure culture from circulating blood. Death—no necropsy.*

D. W. C., Jr., (Med., 19897) a horseshoer, aged 26. Second attack of gonorrhœa, 9 weeks before entry. Three weeks later, pain, swelling and redness in right knee-joint, and later in the muscles of the legs and right big toe-joint. Headache. Recurring chills and fever. Shortness of breath. Præcordial pains. Cough.

Entered the hospital on 13/VII/'06, six weeks after the onset of the arthritis. At this time there was remittent fever (99°-103.8°) and leucocytosis (16,200-32,800). The heart was somewhat enlarged. Loud, roaring systolic murmur at the apex, transmitted outwards, with a diastolic murmur along the left border of the sternum; to and fro murmur in aortic and pulmonary areas; collapsing pulse. There was no urethral discharge. The urine showed a trace of albumin, occasional granular casts and a few red blood corpuscles in the sediment. The spleen was not palpable. There were no petechiæ.

Gonococci were isolated in pure culture from the circulating blood. Anti-gonococcus serum was administered without result.

The patient became very dyspnœic; the anæmia increased. On 24 July, 7-8 weeks after the onset of his symptoms, the patient lapsed into unconsciousness and died. Necropsy refused.

CASE VI. *Gonorrhœa. Vegetative and ulcerative aortic endocarditis. Cultures from blood during life, negative. Gonococci bacterioscopically in valvular vegetations.*

J. C., (Med., 20061; Path., 2765.) A coloured labourer with an history unimportant excepting in that, three weeks before, he had had a swollen ankle. Urethral discharge for two weeks. At about the time of onset of his urethritis was seized with a chill, præcordial pain, general weakness, headache and fever. On admission on 20/VIII/'06, he was a healthy looking man with high fever, rapid pulse and a heart, slightly enlarged with a well marked systolic thrill at the apex, a rather flapping first sound and a loud, rough systolic murmur followed by a faint diastolic rumble, more intense in the aortic area and along the left sternal margin. Pulse, collapsing. Liver three fingers' breadths below the costal margin. Spleen, not felt. The leucocytes ranged

from 28,700 to 40,100 per cu. mm. Anæmia (R.b.c., 3,404,000; hb., 50%). The urine showed a trace of albumin; hyaline and granular casts. The temperature was remittent and sharply intermittent, ranging from normal to 105.6°. The patient failed steadily and died on 10/IX, about 5 weeks after the onset of his symptoms. Cultures from the circulating blood (blood agar and litmus milk) were negative on four occasions.

At *necropsy* the pericardial cavity contained about three times the normal amount of fluid. The endocardium of the left ventricle close to the aortic valve showed a few scattered yellowish-white vegetations. The three cusps of the aortic valve were greatly distorted, thickened and covered with an irregular mass of fragile yellowish-white vegetations. A few scattered vegetations were also seen on the intima of the aorta posteriorly and scattered over the intima of the ascending arch. Anæmic infarcts of spleen and kidneys. Cloudy swelling of all the viscera.

Smears from vegetations on the aortic valve showed Gram-negative diplococci, morphologically and tinctorially gonococci. Cultures from the pericardial fluid and heart's blood, negative.

Diagnosis: acute gonorrhœal endocarditis.

Case VII. *Gonorrhœal urethritis—cystitis—endometritis—salpingitis. Vegetative and ulcerative aortic and mitral endocarditis. Pericarditis. Vegetative aortitis. Mural endocarditis. Pure cultures of gonococci from circulating blood and pericardium during life.*

C. C., (Med., 21977; Path., 2981) a house-maid, aged 21, gave birth on 25/XI/'07, to a full-term child. Two days later, despite the presence of a fever of 102°, she rose from bed and insisted on going to work. Fever continued. Extensive vaginal and urethral discharge. Finally, she was admitted to the gynecological service where she developed a pericarditis. On entrance to the medical side on 19 Dec., she was very anæmic (R.b.c., 2,320,000; leucocytes, 29,560; hb., 41%). There was an intense pericardial friction and a loud to and fro murmur in the aortic area. The friction murmur almost obscured the other cardiac sounds. There was a chronic arthritis of the left hip-joint with a discharging sinus. The temperature was continuous, 99.2°-102.4°; the pulse rapid. The urine showed considerable albumin, many leucocytes and occasional red corpuscles.

Cultures from the blood on the day after entry showed, on blood agar plates, many small colonies which proved to be characteristic gonococci.

The patient failed rapidly. On 24/XII a cloudy fluid with Gram-negative diplococci was obtained from the pericardium. On Christmas day, about 8 weeks after the onset of her symptoms, she died.

The *necropsy* showed a sub-acute gonorrhœal urethritis, cystitis, endometritis, and salpingitis. There was a sub-acute fibrinous pericarditis with effusion, and bilateral pleurisy. Along the line of closure of the mitral valve there were 3 pin-point, grayish elevations. The posterior aortic cusp was covered by a large gray mass about the size of a terminal phalanx of one's finger, which was very friable. On the left cusp there were several masses of similar appearance and consistency measuring several millimeters in diameter; these were also seen at the base of the aorta and on the ventricular endocardium near the aortic orifice. The kidneys were enlarged, cortex thickened and pale. The liver was rather large, and showed evidences of central necroses and degeneration.

Smears from the aortic vegetations, pericardial and pleural fluids, tubes and endometrium showed gonococci which were also found but in small numbers in an area of bronchopneumonia.

Case VIII. *Vegetative and ulcerative endocarditis of mitral and aortic valves—Arthritis. Multiple embolisms. Gonococci obtained in pure culture on two occasions from the circulating blood and demonstrated morphologically and tinctorially in the valvular thrombi.*

H. B., (Med., 22529; Path., 3050.) a negro aged 25, denying venereal disease, had been seized 7 weeks before entry with a chill, and on the following day, with pains in his knees and legs. This had been followed by fever and a slight cough. From the onset he had been obliged to stay in bed.

On admission on 24/IV/'08, he was a well developed coloured man, not especially anæmic (R.b.c., 5,300,000; hb., 72%); there was a marked leucocytosis (19,300) and high fever with rapid pulse. The heart was a little enlarged. There was a palpable systolic thrill. At the apex the first sound was replaced by a high-pitched, long, blowing murmur; second pulmonic, accentuated. The temperature ranged from subnormal to 105°; sharp intermittent paroxysms. Urine: sp. gr., 1015-1020; trace of albumin; in the sed., hyaline and epithelial casts and occasional red blood corpuscles. The leucocytosis increased, reaching at one time, 33,900. On the first of May there was a severe nose-bleed. On 2/V small conjunctival ecchymoses appeared. On the same day there was a sudden loss of power on the left side with increased reflexes. A diastolic murmur developed along the left border of the sternum. The patient failed rapidly, the urine became scanty, the pulse, more rapid, and on 2/V, about 8 weeks after the onset of his illness, he died.

Gonococci were twice obtained in pure culture from the circulating blood. At necropsy there were numerous subepicardial hæmorrhages. The mitral orifice was almost plugged by a large thrombus attached to the right half of the aortic cusp, measuring 2.5x1.5 cm.; there was another mass of about the same size on the left half of the ventricular cusp of the valve. Many of the chordæ tendineæ were covered with small, translucent, wart-like growths as were the papillary muscles supplying these chordæ. About 1 cm. above the point of attachment of the mitral valve on the endocardium of the auricle, there were several wart-like vegetations. On the posterior aortic cusp was a small thrombus mass attached by a pedicle. There were multiple emboli in the brain. Anæmic infarcts in the kidney, conjunctivæ, heart and muscles. Kidneys, large, showing marked parenchymatous degeneration. Morphologically and tinctorially gonococci were demonstrated in the thrombi on the valves.

Case IX. *Vegetative and ulcerative endocarditis of aortic and tricuspid valves. Gonococci obtained in pure culture from the circulating blood and demonstrated microscopically in the valvular thrombi.*

W. W., (Med., 25152; Path., 3337.) a coloured janitor, began on 31/XII/'09 to suffer from fever, exhaustion, cough with considerable expectoration, sweating at night. At the end of a week he was so feeble that he went to bed. On entry, two weeks after the onset of his symptoms, there was high fever, rapid pulse, marked leucocytosis, ranging, during his illness, from 15,240 to 33,600; moderate anæmia (R.b.c., 4,684,000; hb., 75%), albuminuria and cylindruria.

Heart, slightly enlarged; the first sound at the apex, booming followed by a loud systolic murmur transmitted to the axilla; faint diastolic heard along the left sternal margin. Pulse, rapid and collapsing. Liver, enlarged, 2 cm. below the costal margin. Culture from the blood on entry negative.

The patient steadily failed. There was high remittent and intermittent fever and increasing rapidity of the pulse. On 19 Jan., cultures from the blood by Dr. Guthrie showed characteristic gonococci. Sudden death on 21/I about three weeks after onset of symptoms.

Necropsy: Just at the attachment of two cusps of the tricuspid valve, below the foramen ovale, was a wart-like vegetation, friable and firmly adherent to the wall. A few small vegetations on left coronary cusp of the aortic valve. The right coronary and pos-

terior cusps of the aortic valve showed large excrescences and ulcerations one of which had extended backward for some distance into the heart wall. There was an acute diffuse nephritis; splenic infarction; bilateral hydrothorax. Bacterioscopically, gonococci were found in the smears from the thrombi.

CASE X. *Gonorrhœal vaginitis, metritis, salpingitis, pelvic peritonitis. Hemiplegia. Vegetative aortitis. Blood cultures, negative. No bacteriological examination at necropsy.*

G. W., (Surgical, 27762; Path., 3556.) a coloured girl aged 9. Five days before entry, pain in the lower abdomen and about the umbilicus with cramp-like exacerbations; vomiting. Entered the hospital on 9/V/'11 with severe abdominal pain, moderate distention, tenderness and muscle spasm. Temperature, 99.8°. Physical examination, otherwise negative. Leucocytes, 10,000-12,000. Purulent vaginitis with Gram-negative intracellular diplococci, morphologically characteristic of gonococci. Irregular remittent fever (99-102°), slowly rising.

22/V. The patient suddenly became stuporous, did not answer questions; tossing the head from side to side; pupils dilated; reflexes, exaggerated, ankle clonus; Babinski, positive. Lumbar puncture, clear fluid. Pulse, irregular. Loud systolic murmur in the pulmonary area.

24/V. Reflexes exaggerated on the left; rigidity more marked on the right. Abdominal reflexes, absent. Blood cultures and cultures from the spinal fluid negative. The pulse became steadily more rapid, the leucocytes increased to 13,000 and on June 1 the patient died. The specific gravity of the urine varied from 1005-1016; there was a trace of albumin; epithelial and pus cells in the sediment.

Necropsy: Acute urethritis, vaginitis, cystitis, pyelitis, endometritis, bilateral salpingitis; acute and chronic pelvic peritonitis. Heart valves and orifices showed no abnormalities. In the aorta "just above one of the sinuses of Valsalva is a small, round area, 4 mm. in diameter, on which the intima is lost and the wall covered by soft friable grayish material which extends into the lumen of the artery, 2-3 mm." . . . . . Brain: "The basilar artery, posterior cerebrals and the right middle cerebral artery and some of its branches are occluded by red friable casts. The carotids, left middle cerebrals and anterior cerebrals are empty." . . . . . On the right, "the upper surface of the caudate nucleus, in its anterior third, is found to be soft and of a rather hæmorrhagic appearance. There is no large blood-clot, however, and the blood seems to be mingled with the softened brain tissue. On section through the brain this softened area appears to be about 3 cm. in lateral diameter and to extend for 7-8 cm. antero-posteriorly, involving the caudate nucleus and the tracts just outside."

CASE XI. *Gonorrhœa. Vegetative and ulcerative endocarditis of pulmonic valves. Acute nephritis. Gonococcus obtained in pure culture from circulating blood.*

G. R., (Surgical, 35320; Path., 4222.) a man of 27 with no history of gonorrhœa, began, about 7 months before entry, to suffer from general weakness, submaxillary swelling on the left side, fever, abdominal pains and, a week later, chills recurring at irregular intervals. Blood cultures at this time were negative. Fever, irregular and intermittent, and chills persisted. There was a leucocytosis of from 10 to 15,000. Albuminuria and cylindruria. Petechial eruption.

A slight improvement during the summer was followed by return of active symptoms two weeks before entry on 17/IX/'14. In the hospital he was pale and somewhat emaciated. The heart was a little large. "Over the apex the first sound is sharply replaced by a soft blowing murmur which can just be heard in the anterior axillary line but is much louder and more distinct over the second and third intercostal spaces just at the left sternal margin."

Nov. 2. "Over the præcordium a soft diastolic murmur can be heard; this murmur is sharply localized to the area over which the systolic murmur was heard on admission and follows the latter murmur, replacing the second heart sound."

Spleen, large and palpable. Liver, 2 cm. below the costal margin. Slight tibial œdema. Petechiæ on different parts of the body. Leucocytes on entry but 8,000, rapidly rising.

Urine showed much albumin; hyaline, granular and cellular casts and numerous red blood corpuscles in the sediment. Phthalein, 13/IX, 41%; 18/IX, 34%.

Repeated cultures from the blood showed numerous colonies of characteristic gonococci growing only on blood agar plates.

The anæmia increased. There was tenderness over the spleen. Transfusions gave no permanent relief. There was an annoying diarrhœa. The blood pressure generally varied from 110/70 to 105/60, rising so ;what after the transfusions. On one occasion it fell as low as 80/40.

Death, 11/XI/'14, more than 8 months after the onset of his symptoms.

At *necropsy* there was found a chronic urethritis, cystitis, orchitis, pyelitis. Numerous minute ecchymoses in the epicardium. The pulmonary valve showed large vegetations which were friable and definitely attached to the edges of the valve; the valve substance itself was apparently eroded in places where the vegetations were not present and the free edges of the valve were rolled and thickened. Acute hæmorrhagic nephritis. Central necroses in the liver. There was no note in the autopsy records as to cultures *post mortem*, but the pathological diagnosis was: "Gonococcus septicæmia and endocarditis."

CASE XII. *Gonorrhœa. Chronic urethritis. Prostatitis. Vegetative and ulcerative endocarditis of aortic valve. Cultures from the blood during life, negative.*

H. P., (Med., 42732; Path., 6061) a coloured laborer, aged 23, three weeks after the onset of a gonorrhœa which he thought had cleared up, began to suffer from severe headaches followed, a week later, by smothering sensations at night. There was diarrhœa and some slight stiffness of his joints.

On entering the hospital (11/XI/'19) he was a healthy looking young coloured man with a temperature of 103° and a rather rapid pulse. The heart was a little enlarged; there was a soft, blowing diastolic murmur along the left sternal border and in the aortic area, and, at the apex, a rumble in diastole ending in a loud, ringing first sound. The pulse was collapsing. Neither liver nor spleen was felt. There was a leucocytosis of 19,760. The fever was remittent, between 100.8° and 103.8°. The urine showed a trace of albumin; hyaline casts and an occasional red blood corpuscle in the sediment. Spleen, not palpable. Cultures from the blood and urine were negative. Spinal puncture was negative. On the 15/XI he had a sharp, shaking chill. The patient failed steadily. The respiration became rapid and shallow. Signs of broncho-pneumonia appeared, and on 18/XI he died.

At *necropsy* there was found a chronic urethritis and prostatitis. On the mesial cusp of the aortic valve and ascending into the sinus of Valsalva behind it was a large soft pink friable vegetation; the cusps of the valve had almost been eroded away and leading from the sinus of Valsalva was a deep ulceration extending through the base of the aorta into the tissue of the right auricle and ventricle; this ulcerated excavation was filled with recent thrombus and formed a bulging mass partially occluding the tricuspid valve which was adherent to the protrusion behind it. The chordæ tendineæ of the tricuspid were somewhat shortened and thickened.

There were small areas of lobular pneumonia in the lower lobe of the right lung.

Most unfortunately, owing to a misunderstanding, no bacteriological examinations were made at necropsy.

CASE XIII. *Gonorrhœa. Arthritis. Irregular remittent and intermittent fever with chills. Cardiac enlargement with evi-*

dence of mitral disease. Splenic enlargement. Leucocytosis. Pleuro-pericardial friction. Cultures from circulating blood, negative. Death seven weeks after onset. Necropsy refused.

W. W. R., (Med., 7505) aged 32. Gonorrhœa, eight weeks before entry, 26/VI/1897. Three weeks later, arthritis of the hip and later of the knees. Two weeks before entry, severe headaches, pain in the back, chills, fever, sweating, nose bleed, frequent vomiting, slight cough. Has been in bed since the onset. On entry he was febrile; the pulse was accelerated; the heart was slightly enlarged. The first sound at the apex was replaced by a loud blowing systolic murmur heard throughout the axilla. Second pulmonic, a little accentuated. Spleen palpable. Five years before, on a previous entry, the heart had shown no abnormalities. There was a purulent urethral discharge containing diplococci. Leucocytes, 21,000. There was high, irregular, remittent fever. The leucocytes rose to 23,000. The first heart sound became loud and very snapping; the murmur changed considerably in character from day to day. A pleuro-pericardial friction rub appeared. The patient steadily lost ground and died on the 2/VIII, seven weeks after the onset of his symptoms which were obviously those of an acute ulcerative endocarditis.

Necropsy, refused.

POST-ENCEPHALITIC BEHAVIOR DISORDERS IN CHILDREN

By Leslie B. Hohman

(From the Henry Phipps Psychiatric Clinic, Johns Hopkins Hospital)

For the past year, we have had an opportunity to study 11 children who have been brought to the clinic because of decided, profound changes in character and behavior. In all the cases, the disposition of the child had changed so suddenly and completely, or else been so much altered from its former behavior, that one could not avoid the conclusion that a specific etiological agent was at work. In each of the 11 cases, we have discovered that the change followed an attack of epidemic encephalitis.* From time to time our feeling that the connection between these alterations and encephalitis was genuine has been strengthened by the appearance of reports in the literature of several similar observations. Happ and Blackfan,[1] Findlay and Shiskin,[2] Grossman,[4] and Francioni,[5] have either noted the change in passing or have mentioned it specifically. Leahy and Sands [3] report six cases to illustrate such a change. We are adding 11 cases to the literature to emphasize the point that the condition is apparently not uncommon, and because we believe that sick children are very apt to be classed merely as bad children and treated accordingly. In addition, certain reactions have been observed which are usually classified as purely functional or psychobiological, which apparently are closely related with the organic alteration. I refer especially to tics and excessive talk. While the main point of the inquiry has been directed toward the behavior changes, we have also noted the changes in sleep, the behavior during the sleepless periods, and the tics and excessive talk already mentioned.

In reporting the case records, we shall omit the details of the original febrile period, giving only enough facts to prove the reliability of the diagnosis. We have tried, when possible, to discover what rôle constitutional factors play in the etiology of the later changes. We have accordingly studied the family history for mental disturbances, and the individual's for neurotic traits (night terrors, enuresis, thumb-sucking, tantrums, and emotional instability). Our conclusions are not decisive, but the rôle of constitutional factors is certainly not great. Contrary to the belief of Francioni,[5] who found a neuropathic background in all his cases, only two of the 11 children had shown any abnormality before the development of the infection, and in these cases the deviation was only slight —one child was described as having been "stubborn," and another as "more nervous than the other children." The parents of three of the children were nervous or psychotic. There also seems to be little relation between neuropathic background and chance of improvement, as two of the five improved patients had this background. We have thought that the reaction, instead of being due to a specific psychopathic background, might be explainable in terms of a release of a more primitive, instinctive reaction, such as the child shows who is undisciplined and untrained, that is to say, the reaction released is a more general childlike lack of control with no training inhibitions.

Behavior and Character Changes.—The most striking feature of these cases has been the changes in the character and behavior of these children. They became irritable, fussy, quick-tempered, or boisterous and restless. Instead of being able to play peacefully with other children as formerly, they became quarrelsome, teased the other children unmercifully, or showed streaks of brutality. At school, the teachers found them impudent, disrespectful, disobedient, or no longer amenable to discipline. This same disrespectful attitude was also displayed at home; they would curse their parents, or even strike at them. Instead of being interested in the school work and averagely diligent, they became indolent and indifferent. Several of the patients asserted their independence, insisting that they would do what they pleased. One little girl announced that she was now her "own boss." Staying on the street at all hours, and running away from home have been frequent. Some of the patients lost respect for personal and public property: they destroyed their own belongings or the house furnishings.

* The summary of the findings in each case is appended to show on what grounds the diagnosis was made.

They were frequently negligent about their personal appearance, slovenly, taking off their clothes in public, and were careless with their excreta, in some cases even playing with them. One of our children smeared with feces the walls and the face of her brother. Several have shown exhibition tendencies (showing the legs, leaving the trousers open, etc.), and one observer [3] reports extraordinary sexual precocity in a boy of 8½, who attempted intercourse with his mother. Not infrequently patients were found fabricating or lying. The temper tantrums sometimes became so dangerous that everyone in the vicinity was in danger. Others had screaming attacks which were uncontrollable. Some of the children became emotionally quite unstable, weeping on the slightest provocation, were capriciously moody, or very irritable, fussy, whiny, and excitable. Discipline was simply resented and was quite ineffectual.

Grossman [4] reports one interesting case, in which this order of events was reversed. A very unruly child became docile and well-behaved following the encephalitic attack.

Sleep Alteration.—The sleep alteration, as described by various observers, [1 to 9] is strikingly uniform. The children found it impossible to go to sleep when they were put to bed, but generally would stay asleep very late on the following day. Waking the children early in the morning, or trying to tire them through strenuous exercise, did not aid them in getting to sleep the following night. Sedatives, in the cases we have had an opportunity to observe, have had a variable effect. At times a dose of barbital or paraldehyde would compel sleep immediately, whereas on the very next occasion it would prove useless. We cannot subscribe to Rütimeyer's [9] conclusion that "the insomnia yields to psychotherapy unless there is evidence of persisting organic lesions." Psychotherapy has been entirely unavailing in our hands, although a number of our children showed no persisting signs of organic lesion.

The behavior during the sleepless periods has been characteristic. The child, as soon as it went to bed, would begin to be very restless, uneasy, and talkative. The talk would be continuous, but show no distortions. In some cases, the restlessness took the form of compulsive movements, of which we shall speak later. At times, the patients would sing or whistle, or become playful and prankish.

Over-talkativeness.—While over-talkativeness during the nocturnal insomnia has been quite common, a few of the children have shown the same feature during the daytime. This push of talk without distortion has been observed in adults,[10] and has been recorded in children by several observers, although not specifically noted [1, 2, 3]. Only one of our patients showed this symptom (Case 7).

Tics.—The compulsive, purposive, habitual movements at first impressed one as indistinguishable from the usual tics which have been so uniformly explained as purely functional. This point of view has not been accepted by all observers, however. Adolf Meyer has repeatedly expressed the view that in stammering, in addition to the emotional factors involved, there was also a defect of the actual speech mechanism.

It would seem that the frequency of occurrence of these movements in this disease must point to some uniform organic basis behind the activity. What this is, we do not know. The following is the list of obsessive movements observed in the different cases: spitting, nose picking, lip picking, forced respiratory movements, touching the shoe and putting the hand in the mouth, wetting the finger and rubbing the cheek and ear with it, shaking the hand, making the sign of the cross, smoothing the hair, making signals, clicking movements of the tongue, clearing the throat, stretching the arms laterally in rhythms of some multiple of three, nose wiping movements, and others. Of these the spitting was probably the most common.

Therapy.—We have discovered nothing that is of any value in the treatment of these patients. Time seems to be the sole healing factor. The problems presented are at times very serious, as it is often impossible to maintain the children in their home environment, because of the behavior difficulties. Some of the children have been sent to hospitals for the insane, others to schools for incorrigible children. It has been the regular experience that *punishment helps not at all.* Nevertheless, we have persisted in our recommendations of a moderately rigorous regime, since we found that too lax treatment might tempt the child to use "doctor's orders," as an excuse for disobedience or misbehavior.

Prognosis.—The earlier reports give very guarded or bad prognostications. Our experience has made us more hopeful. We have seen complete recovery in 2 cases after 9 months and 3 years; marked continuous improvement in 4 cases after 6 months, 1½ years and 2 years, and 2 years; slight improvement in 3 cases after 3 years, 1¾ years, and 1½ years; and no improvement in 2 cases both with a duration of 1½ years. Over half of our patients, then, have shown marked improvement or recovery.

CASE REPORTS

CASE 1.—D. D. The patient, a colored girl of 11, was brought to the clinic because since March 1st, 1920, after an attack of epidemic encephalitis, she had become utterly unmanageable at home and in school. Although a somewhat stubborn child, she was not regarded as abnormal. Since her illness she had done very poorly at school because she would neglect her work for idle reading. When she was crossed in any way she would become very disrespectful to her mother and teacher, and if the children at school offended her, she knocked them down. It had been found necessary to remove her from two schools because of her cruelty to the other children. At nights she was very restless, and would talk and thrash about in her sleep.

She had to be committed to a hospital for the insane. A report later describes her as much improved.

Case 2.—D. C. The patient was a white girl of 13½, who was brought to us on March 9, 1921, because of change in disposition, irritability, and quick temper, following an attack of epidemic encephalitis, in Dec. 1918. Her convalescence was protracted (4 months) and during this period her mother noticed that the child was fussy and irritable, noisy, boisterous, and sang loudly. Finally she had to be removed from school because she idled and fought constantly with the other children. In June she became much worse, cursing her mother, and finally ran away from home. She became slovenly about her person, and careless about her excreta. Recently she had improved in the latter respect. She slept very poorly and would talk most of the night.

She had finally to be sent to a disciplinary school.

Case 3.—W. S. The patient, a white boy of 13, was brought to the clinic Feb. 23rd, 1921, because of restlessness and sleeplessness, following an attack of epidemic encephalitis in April, 1920. Since the attack the boy has no longer been friendly and outgoing, but wants to sit by himself and read. He takes no interest in playing with the other children. At nights he is sleepless and restless, and as soon as he gets into bed, he begins to spit, picks his nose, and complains that he cannot get his breath. He does not go to sleep until one o'clock in the morning and then sleeps until noon the next day. Waking him earlier in the morning does not improve his sleep at nights.

Recently he has shown marked general improvement.

Case 4.—L. R. A white boy, aged 9, was brought to the clinic, Sept. 30, 1921, because of nervousness, screaming spells and irritability, following an attack of epidemic encephalitis in Sept., 1919. Since his 3 weeks' acute illness, he has had uncontrollable screaming spells both at night and in the daytime. He has become very nervous and irritable, and will not be disciplined. Punishment does not seem to influence his behavior. In Jan., 1920, he began the habit of touching his shoe and putting his hand in his mouth, in a tic-like manner.

Recently he has begun to show improvement in all his activities.

Case 5.—A. M. A white boy, aged 8, was brought to the clinic Oct. 11th, 1920, because of sleeplessness, and "funny talking" at night, which came on following an attack of epidemic encephalitis in Jan., 1920. After the acute infection the boy became very restless when put to bed. He began to puff and then scream, wept, ran from room to room, tearing at his clothes, etc. He could not get to sleep until very late and then went to sleep the following day in school. He preferred to stay at home and "play in water." He fought with the other children, refused to obey his mother, and was generally impudent. He became careless about his clothes and allowed his trousers to remain unfastened. He drooled saliva, spit constantly, and chewed his handkerchief.

His behavior has improved somewhat lately, but not much.

Case 6.—A. S. A white girl, aged 8 years, was brought to the clinic Jan. 8th, 1921, for "restlessness at night," following an attack of acute epidemic encephalitis in June, 1920. After the first month of the illness she began to sleep very little at night and was very difficult to arouse in the morning. In Oct., 1920, she began to wet the bed at night and her mother found her sitting up in bed "breathing hard." In Sept., 1921, the child was brought to the clinic again because she had become very destructive, tearing up her copy-books, pulling off the wall-paper, and throwing water around the house. Two weeks before we saw her she had smeared the wall, the bed, and her brothers' faces with feces. At school she is reported to be using "bad language" and cursing. She shows violent temper tantrums and has announced that she is her own boss. She can no longer play with other children, because she quarrels with them and abuses them. Punishment avails nothing. All this is all a total reversal of her former behavior. She was a very healthy, affectionate child and was very obedient.

Up to date no improvement has been reported.

Case 7.—G. R. A colored girl, 13 years of age, was brought to the clinic on April 8, 1921, because of "absent-mindedness and no memory," following an attack of epidemic encephalitis in February, 1921. Immediately following the acute attack (two weeks), the patient would sit quietly by herself, making revolving motions with her hands and laughing in a silly manner to herself. She slept poorly and did not want to go to bed at night. She refused to obey her father and was very resentful to him. If he touched her, she got angry, and fought him. She had become very careless of her personal appearance, allowing her stockings to hang down, exposing her legs before boys, etc. She had no ambition to return to school. By June, 1921, the irritability and insomnia had disappeared, but she talked very little. It was noticed that she picked her nose and lips excessively. Her appetite had become huge. In August, she began to talk more and more, until by September she was over-talkative and very over-active and playful, teasing her mother and father.

In October, 1921, she was practically her old self.

Case 8.—K. S. A white boy, of 14 years, was brought to the clinic September 29, 1920, because of a "lump in the throat and constant spitting," following an attack of epidemic encephalitis in February, 1920. He had slept constantly during March, but in April he became sleepless and restless, talking incessantly at night. He began to spit obsessively and complained of a lump in the throat. Then appeared various tic-like movements:—wetting his fingers and then rubbing his cheeks and ears. He would laugh very readily and without adequate cause.

Up to date, there has been no improvement in his behavior.

Case 9.—M. W. A white boy, of 12, was brought to the clinic March 16, 1921, because of "incorrigibility" following an attack of epidemic encephalitis in January, 1919. The following spring and summer he was very sleepy all the time, spent most of his time lying about the house, and wept over almost anything. Since the summer of 1919, he has been very restless and feels he must be in motion constantly and, if hindered, becomes fussy and whiny. He became incorrigible at school, was impudent, "talked back," and was very resentful over discipline. He played truant frequently, and on several occasions stayed away from home all night. His mother hoped that discipline would help him, and had him placed as a ward of the juvenile court. However, neither this nor the application of corporal punishment helped. In August, 1920, he began to show some improvement, and was better behaved at home. At present, he is still more improved, and is doing very well at school, having been promoted twice. His I. Q. at the first examination was 87; it is now 100.

Case 10.—T. C. A white boy, 9 years old, was admitted to the clinic June 12, 1920, from the Harriet Lane Home for Invalid Children, because of restlessness following an attack of epidemic encephalitis in October, 1919. Following the pyrexial attack, he began to sing and whistle constantly, became unruly, refused to eat and made odd movements with his hands and legs. During January, 1920, the patient would refuse to stay in bed, and wanted to be on the street all night. He removed his clothing while on the street, but replaced it when told to do so. His restlessness and irritability increased, and he was brought to the hospital. In the hospital he showed very odd restless movements, which he would repeat over and over, crossing himself, smoothing his hair, making signals, and queer clicking movements with his tongue. Nothing could control these movements. He sang and whistled all the time. He slept very badly and was very irritable and capriciously moody.

Up to August, 1921, there had been no change in his condition.

CASE 11.—P. E. A white boy, 10 years old, was admitted to the clinic May 19, 1920, because of restlessness, sleeplessness and stereotyped movements, following an attack of epidemic encephalitis in February, 1920. The boy made what appeared to be an excellent recovery from the acute attack in 3 weeks, although he complained of a fullness in the throat. Soon it was noticed that he was "nervous," fidgety, and could not sleep at night, although he slept well in the day time. He talked all night, but all his talk was sensible. He began to repeat certain complicated movements over and over. (1) He would take a deep breath, then expel it with a short cough. (2) He would stretch out his arms two or three times in rapid succession. The leg also was used at times. These movements seemed to relieve some indefinite discomfort. (3) He put his finger to his nose, with a wiping movement. These movements were repeated constantly with a rhythmicity of three or a multiple of three. While in the hospital here, he demanded constant attention, was very restless, and questioned everything that was done for him. He quarrelled frequently with another child on the ward. He would weep on the slightest provocation. While in the clinic, he developed a spitting tic. His sleep at night was very poor. Previous to the onset of his illness, he had been entirely normal.

On discharge, July 4, 1920, he was decidedly improved.

CONCLUSION

1. Definite character changes are sequelæ of epidemic encephalitis.
2. The alterations of sleep and the activity during wakefulness are characteristic.
3. Tics have been so frequently observed as to warrant the search for a structural background.
4. Therapy seems to be useless.
5. Over half of the reported cases have improved.

DATA UPON WHICH THE DIAGNOSIS WAS BASED

CASE 1. Fever, ptosis, and typical spinal fluid alterations.

—2. Fever, diplopia, somnolence, left-sided weakness.

—3. Fever, right internal strabismus, restlessness, sleeplessness, odd behavior with delirium.

—4. "Flu," fever, delirium. Bi-lateral ptosis.

—5. "Flu," with sleeplessness, double vision and fever.

—6. Fatiguability, lethargy, fever, then sleeplessness.

—7. Fever, delirium, drowsiness, headaches, nocturnal excitability.

—8. Fever, drowsiness, constant sleep, Parkinsonion rigidity.

—9. "Flu" with drowsiness, lethargy, and drowsiness.

—10. Fever, insomnia, restlessness, spinal fluid findings typical.

—11. Fever, delirium, muscular jerkings, insomnia, and typical spinal fluid findings.

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TOLERANCE AND ACQUIRED TOLERANCE OF THE MESENCHYME CELLS IN TISSUE-CULTURES FOR COPPER SULPHATE AND SODIUM ARSENITE

By JULIUS LANE WILSON

(From the Carnegie Laboratory of Embryology, Johns Hopkins Medical School)

Natural tolerance and acquired tolerance exhibited by an organism for toxic substances may depend upon the neutralization of the toxin by extracellular substances or upon some intracellular mechanism; that is to say, the toxin is either neutralized without or within the cells of the organism. In dealing with the entire organism it is impossible, in most instances at least, to determine whether the phenomenon is intracellular or extracellular. In tissue-cultures, on the other hand, as with some of the lower organisms, there is the possibility of testing directly the tolerance of cells for toxic substances. Unicellular organisms tolerate certain poisons and even develop an acquired tolerance or immunity for concentrations above the lethal dose.

Davenport and Neal (1896) * found that Stentor cœruleus, a unicellular organism, after being kept for a few days in a weak solution of corrosive sublimate, was able to survive a stronger solution several times as

* Davenport, C. B. and H. V. Neal, 1895. Acclimatization of organisms to poisonous chemical substances. Arch. f. Entwcklngsmech. d. Organ, II, 564-583.

long as a control animal of the same series. Daniel (1909) ‡ found that certain strains of Stentor cœruleus and Spirostomum ambiguum, unicellular forms, after living for a few days in 1 per cent ethyl alcohol, had increased resistance to stronger solutions, as shown by the fact that the organisms were not killed so quickly in a lethal solution and that many continued to live in a stronger solution than that in which they could have lived before "acclimatization." One strain of Stentor did not develop an acquired tolerance. There was no observed development of acquired tolerance for hydrochloric acid or sodium hydroxide. With a weak solution of alcohol (1 per cent) the beginning of acclimatization (acquired tolerance) was usually evident within a few hours. This increased in a fairly uniform ratio until about the fourth day, at which time the maximum degree of immunity might be expected. Daniel found that a one per cent solution of the alcohol gave greater tolerance than a half per cent solution, while stronger solutions decreased the resistance by producing injury to the organism.

Concerning the ordinary embryonic mesenchyme cells of the chick embryo, the following experiments will show that they have a certain amount of tolerance for the two inorganic poisons used and that an increased or acquired tolerance can be produced by cultivation in weak solutions of these substances. In testing the degree of acquired tolerance, the cultures were washed with several drops of the solution in such a manner that the practically undiluted solution must have bathed the cells, and any neutralizing substances produced by the cells during their cultivation in the weak or immunizing solutions were entirely washed away.

The cultures were made in the usual manner from tissues of 7 to 11 day chick embryos. Locke-Lewis solution, namely 85 c.c. of Locke solution (NaCl .9%, $CaCl_2$ .024%, KCl .042%, $NaHCO_3$ .02%), 15 c.c. of chicken bouillon and 0.5 gm. of dextrose, was used. The observations were confined, for the most part, to the ordinary mesenchyme cells from the subcutaneous tissue and from the lungs. Stock solutions of copper sulphate and sodium arsenite in distilled water were added in appropriate amounts to the culture medium. Several series of cultures, varying from 5 to 10 in number, were made for each solution tested and at the same time about the same number of controls were made, using tissue from the same embryo.

The effects of the poisons were measured (1) by comparing the percentage of cultures which showed growth or migration, the size of the growth (in a rough way), and the maximal duration of life with the controls; (2) by comparing the time required to kill cells that were cultivated in these weak solutions with the time required to kill the cells in the controls when treated with strong solutions. The first group gave some idea of the natural tolerance, the second the acquired tolerance.

‡ Daniel, T. F., 1909. Adaptation and immunity of lower organisms to ethyl alcohol. J. Exper. Zool., VI, 571-611.

Experiments with Copper Sulphate

With a 1 to 25,000 solution no growth or migration was obtained. In six series with a 1 to 50,000 solution, 50 to 80 per cent of the cultures, with an average of 66 per cent, showed migration. The controls averaged 90 per cent. The control cultures were larger. The maximum life of the copper sulphate cultures varied from 5 to 12 days with an average of 8 days, while the average for the control was 13 days. In seven series with a 1 to 100,000 solution, from 30 to 100 per cent grew, with an average of about 60 per cent. The controls averaged 94 per cent; they were larger, as a rule, than the copper sulphate cultures. The maximum duration of life of the copper sulphate series varied from 4 to 11 days, with an average of about 7 days. The maximum for the controls varied from 8 to 11 days.

In order to test the acquired tolerance, normal 2 and 3 day cultures were first stained for 10 minutes in a weak solution of neutral red and janus green and then washed with a 1 to 5,000 solution of copper sulphate in Locke's solution. It was found that cells lived from 17 to 38 minutes, averaging about 26 minutes. The death changes were characterized by coagulation and swelling, with increased visibility of the nucleus, which became sharply outlined by what appeared to be a nuclear membrane. Accompaning these nuclear changes was loss of the greenish color from the mitochondria and the red color from the degeneration granules. The nucleoli often became stained. After death the whole cell was sometimes diffusely stained. Accompanying all these changes, which began about 10 minutes after the application of the copper sulphate, was a vacuolization of the cytoplasm.

Cultures that were made at the same time with 1 to 100,000 copper sulphate in Locke-Lewis solution were treated in the same manner with a 1 to 5,000 solution of copper sulphate. The death changes were similar and the cells were considered dead in from 25 to 56 minutes. The average time was 42 minutes. As compared with the average time for the normal cultures of the same age, 26 minutes, this indicates that the cells acquired a considerable tolerance for the copper sulphate.

Experiments with Sodium Arsenite

In the 1 to 50,000 solution of sodium arsenite there was no growth. In one series with 1 to 100,000 solution, about 50 per cent of the cultures showed migration as compared with 85 per cent of the controls. Their maximum life was 1 day as compared with 9 days for the controls. In two series with a 1 to 200,000 solution, about

30 per cent showed migration as compared with 80 per cent for the controls. Their maximum life averaged 3 days as compared with 9 days for the controls. In seven series with a 1 to 250,000 solution, from 60 to 100 per cent of the cultures showed migration, with an average of 77 per cent, as compared with 90 per cent for the controls. The average maximum duration for the seven series was 6 days as compared with 8 days for the controls. In three series with a 1 to 500,000 solution, 88 per cent showed growth as compared with 86 per cent for the controls. Their average maximum life was 6 days as compared with 9 days for the controls.

To ascertain the acquired tolerance, normal 3 to 6 day cultures, after 10 minutes staining with a weak solution of janus green and neutral red, were washed in the usual manner with a 1 to 10,000 solution of the sodium arsenite. Cell death occurred in from 22 to 50 minutes, averaging about 33 minutes. Cultures of the same age, growing in the 1 to 250,000 solution of sodium arsenite, showed cell death in from 39 to 70 minutes, averaging about 53 minutes. The death changes were somewhat similar to those in the copper sulphate experiments, except that the nucleus became shrunken and more highly refractive.

CONCLUSION

Embryonic mesenchyme cells, cultivated in weak solutions of copper sulphate and sodium arsenite, develop in the course of two days an acquired intracellular tolerance for strong doses of these two poisons.

NOTE ON THE ABDOMINAL CHROMAFFIN BODY IN DOGS

By GEORGE B. WISLOCKI and S. J. CROWE

(From the Department of Anatomy and Surgery of the Johns Hopkins University)

In 1914 we [3] published the results of some experiments on the suprarenal glands in dogs, with especial reference to the functions of the interrenal portions, reaching the conclusion that it is the cortex rather than the medullary portion that is essential to life. In that series suprarenal insufficiency was produced by repeated surgical operations; during the past year we have tried to produce a suprarenal insufficiency by a combination of surgical removal and implantation of radium.†

Our previous experiences had shown that if half (and in some instances as little as one quarter) of one suprarenal gland is left in place, the remaining portion, together with the other gland, may be removed without seriously disturbing the health of the animal. During the past year another series of experiments was carried out. In these we removed one suprarenal gland and from one quarter to three quarters of the other, and at the operation implanted capillary glass points, containing radium emanations in varying amounts, into the portion of the gland that remained. From a total of 16 dogs treated in this manner 10 died, and this note is limited to the description of the changes observed in the abdominal chromaffin body in these 10 dogs.

The investigations of Stilling,[7] Swale Vincent,[8] and Kahn [5] have shown that in the dog, as in many mammals, there is a conspicuous band of more or less continuous chromaffin tissue lying ventral to the abdominal aorta and just beneath the peritoneum.* Vincent and Kahn have made careful anatomical and physiological investigations of this chromaffin body in the dog. It varies from 60 to 80 mm. in length and 2.5 to 5 mm. in width, is slightly less than 1 mm. in thickness, and weighs approximately 0.06 grams. The arteries supplying this body arise directly either from the aorta or the right internal spermatic; the veins empty into the right or left spermatic vein. The cells comprising it give the same brownish reaction with the salts of chromic acid that is so characteristic of the medullary portion of the adrenal. This brown stain is believed to be due to the interaction of the chromic salts with adrenalin. Kohn [6] has pointed out, however, that the cells of the chromaffin body rarely stain as deeply as do the medullary cells of the adrenals.

The physiological researches of Biedl and Wiesel,[1] Vincent,[9] Fulk and MacLeod,[4] and Kahn [5] have demonstrated that a substance identical with the active principle of the suprarenal medulla, may be recovered from the abdominal chromaffin body. Biedl and Wiesel prepared extracts of the human accessory chromaffin tissue (organ

† The radium used in these experiments was given us by the Howard A. Kelly Hospital.

* Stilling was the first to show that the collections of cells closely resembling those of the adrenal medulla, which are associated with the sympathetic nervous system, give a reaction with chromic acid salts, similar to that of the medulla of the adrenal. He called these groups of cells "chromophil bodies." Vincent later changed the spelling to "chromaphil." Kohn [6] introduced the term "chromaffin," and designated collections of these cells as "paraganglia." He directed attention to a conspicuous mass of these cells lying ventral to the abdominal aorta which was constantly present in the mammals investigated by him and which he termed the "paraganglion aorticum abdominale." In the subsequent literature this body has usually been referred to as the "abdominal chromaffin body."

of Zuckerkandl) from new-borns, and found that such an extract has the same effect on the blood-pressure and heart-rate as suprarenalin. Vincent was able to demonstrate that an extract of the abdominal chromaffin body of a dog will produce a rise in blood-pressure when injected into the blood-stream of another dog. He concluded that all accessory chromaffin tissue contains adrenin, or a substance having similar chemical and pharmacodynamical properties. Fulk and MacLeod made physiological observations on a variety of animals and concluded therefrom that "acid extracts of the retroperitoneal chromaphil tissue of man, the dog, the cat, the rabbit, the guinea-pig, the white rat, the calf, the sheep and the pig, have the same physiological action on intestinal and uterine muscle as the active principle of the medulla of the suprarenal glands." Kahn found that extracts of the medullary and of the accessory chromaffin tissue of the dog are identical, in that they both produce a rise in blood-pressure in the rabbit and cat, a mydriatic action in the frog, and a glycosuria following their intravenous injection in the dog. He showed, by accurate determinations of the respective weights of the dog's adrenal medulla and the abdominal chromaffin body, that the latter represents about one-fourth to one-tenth of the total weight of the former. He found, however, that, measured by pharmacological action, the retroperitoneal chromaffin body possesses only one-twelfth to one thirtieth as much active principle as the total adrenal medulla. Furthermore, a given quantity of medulla by weight contains three to four times as much active principle as an equal amount of the chromaffin body. That the chromaffin body contains the same active principle as the adrenal medulla seems to have been amply proved by the work of these investigators.

There remained, however, the question whether or not the abdominal chromaffin body is a functioning organ actually liberating its secretion into the blood-stream. This also Kahn attempted to answer. He collected blood from the veins of the organ, took the serum therefrom and tested its vasoconstrictor action in the hind-legs of a frog by the Trendelenburg method of perfusion, using blood-serum from other veins and the carotid artery as controls. He found a constant difference in respect to the vasoconstrictor action of the employed sera. The serum obtained from the veins of the paraganglia had a stronger and more sustained action than that from the carotid artery or other veins used as controls. Kahn attributes this difference to the presence of a larger amount of blood-pressure-raising substance in the paraganglion veins than in the control veins. That this substance is actually adrenalin seems highly probable from the fact that an increased amount of blood-pressure-raising substance could be demonstrated in the veins of this organ in which adrenalin has been proved beyond doubt to occur.

The method of procedure on the 10 dogs in which we studied the chromaffin reaction of the abdominal chromaffin body is herewith given in condensed tabular form:

TABLE

		Amount of Adrenal Gland left at Operation	Amount of Radium Implanted	Length of Survival
1.	Dog 19	⅕ of 1 adrenal	1-4 6/10 mc. point	24 hours
2.	Dog 22	½ of 1 adrenal	2-1 7/10 mc. point	24 hours
3.	Dog 20	½ of 1 adrenal	2-1 7/10 mc. point	5 days
4.	Dog 16	½ of 1 adrenal	1-4 6/10 mc. point	6 days
5.	Dog 17	½ of 1 adrenal	2-4 6/10 mc. point	7 days
6.	Dog 15	½ of 1 adrenal	1-4 6/10 mc. point	9 days
7.	Dog 18	¾ of 1 adrenal	3-4 6/10 mc. point	14 days
8.	Dog 5	1 entire adrenal	2-7 mc. point	16 days
9.	Dog 21	¼ of 1 adrenal	1-1 7/10 mc. point	21 days
10.	Dog 23	½ of 1 adrenal	1-1 7/10 mc. point	32 days

It will be observed that the adrenal glands were reduced by surgical extirpation to one or a fraction of one adrenal into which fragment radium emanation was then implanted. The animals died at intervals of 24 hours to 32 days following this procedure.

In every instance an autopsy was performed immediately after death. The retroperitoneal tissue suspected of containing the abdominal chromaffin bodies was removed, washed free of blood, and immersed immediately in a mixture of 9 parts of 3.5 per cent potassium bichromate and 1 part of 40 per cent formaldehyde (Kohn's fluid). At the end of 3 hours the tissue was rinsed in tap-water and transferred to 10 per cent formalin for 24 hours for further fixation. It was then washed thoroughly, passed into 60 per cent alcohol and in this latter examined for chromaffin bodies. A small piece of the principal chromaffin body was removed for paraffin imbedding and sectioning, while the bulk of the tissue was bleached in hydrogen peroxide in the sunlight (95 per cent alcohol, 7 parts; water, 1 part; hydrogen peroxide U. S. P., 3 parts) for further demonstration of the microscopically visible chromaffin bodies.

Examination of the abdominal chromaffin bodies in every instance showed a well-marked chromaffin reaction, approximating the color intensity observed in normal animals and indeed occasionally somewhat darker; in no instance was it less intense than in normal animals. No hypertrophy, however, in the sense of an actual increase in number or size of the chromaffin bodies, could be ascertained, either macroscopically or microscopically.

In each instance, histological sections of the principal chromaffin body showed well-preserved cells containing in their cytoplasm an abundance of chromaffin material. Although every section exhibited a typical and well-marked reaction, the picture was not always uniform. In the majority of animals, each cell showed a dark brown reaction, the chromaffin substance completely filling the cytoplasm and occasionally obscuring the nucleus. In a

lesser number, areas were seen in which it was unequally distributed, some cells exhibiting a very deep reaction, while neighboring cells contained clear cytoplasmic vacuoles of various sizes. Such differences in the staining reaction are commonly encountered in the normal adrenal medulla and hence may be attributed to different states of activity on the part of normal cells.

We have found, then, that in dogs in which the adrenals have been destroyed the abdominal chromaffin body at the time of death exhibits a normal or even more intense chromaffin reaction, indicating normal or slightly increased activity on the part of this tissue. Further, we have learned from Kohn that the principal chromaffin body represents one-fourth to one-tenth of the total medullary tissue, but possesses only from one-twelfth to one-thirtieth as much active principle. The problem now arises whether or not this fraction of the total chromaffin tissue represented by the abdominal chromaffin body is capable, in adrenalectomized dogs, of supplying that portion of the function of the adrenal glands subserved by the medulla? While we believe that this question has not been definitely solved, several facts may be cited that tend towards an affirmative answer. One of these is that, at the time of death, the abdominal chromaffin body is found replete with secretion, instead of depleted. However, it cannot be ignored that the chromaffin body could conceivably be found at death to be in a fully functioning state without having fulfilled the minimum requirements necessary to maintain the functional activity of the muscular and vascular apparatus, if, indeed, the secretion of chromaffin tissue contributes to any such important function. Another fact that tends to prove the ability of the chromaffin body to supply the physiological demand for epinephrin is the observation, repeatedly made on other ductless glands (the thyroid, parathyroids, islets of Langerhans, and testes), that only a small fraction of the entire organ is necessary to fulfill the function of the whole.

Perhaps the strongest evidence that the abdominal chromaffin body acts as a substitute for the adrenal medulla is the observations by Biedl,[2] and by the authors,[3] that dogs survive extirpation of the adrenals provided a portion of the cortex only remains.

Is there any evidence as to the relative importance of the cortex and medulla in maintaining life? It seems to us that there is conclusive proof that the cortex is necessary to life, for when, in the above mentioned experiments, the remaining fragment of cortex was removed the animals died. The same experiments prove that the adrenal medulla is not necessary to life, though they by no means demonstrate the same for the entire chromaffin system. The decision that any part of the chromaffin system is or is not necessary to life must rest upon experiments in which the abdominal chromaffin body is removed from animals in which the adrenals have previously been reduced to a cortical fragment. If the animals survive, the necessity of the chromaffin tissue to the maintenance of life could be questioned. It would seem only remotely possible that the insignificant, scattered groups of chromaffin cells remaining would be capable of supplying the function of the chromaffin system. That removal of the abdominal chromaffin body alone, without disturbing the adrenals, is symptomless, has been demonstrated by Kahn. There is great likelihood that the fall in blood-pressure, which is a characteristic symptom of adrenal extirpation, has its origin in the removal of the cortex.

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NOTES ON NEW BOOKS

The Heart, Old and New Views. By H. L. FLINT. Cloth, $4.00. (*New York, Paul B. Hoeber, 1921.*)

Among the many shorter texts dealing with the cardiac irregularities we know of none which presents the subject in the interesting way so successfully attained by the author of this volume.

Written with the two-fold purpose of appealing to those who may have but little time to sift critically the exhaustive literature, as well as for those who desire to turn to the original sources, its value is greatly enhanced by the historical treatment of the subject and by the marginal references to almost all, if not all, the really important literature. The first part of the volume dealing with the heart in antiquity comprises a delightful review of the knowledge of the time of Hippocrates, Galen and Vesalius, and concludes with a study of the period beginning with the discovery of the circulation by Harvey down to recent times. It includes such names as Malpighi, Loeuwenhook, Von Helmont, Descartes and Stenson, and among a host of other equally conspicuous investigators reference is made to the work of James Keill (1673-1719), who was among the first to apply mathematics to the problems of circulatory hydraulics. Part II takes up the development of instruments and instrumental methods, and here again the author is equally successful in his critical analysis and in his appreciation of the fundamental importance of physiology.

The various methods for determining the blood pressure, blood

velocity and output of the heart are referred to briefly. The use of the clinical polygraph, the physiology of the venous curves and the interpretation of the polygraphic records are dealt with in detail, while the subject of electrophysiology and the interpretation of the normal galvanometric curves is soundly discussed and lucidly described. The chapter devoted to a consideration of the five functions of the heart muscle is a concise and clear presentation of the modern conception of cardiac physiology as originally enunciated by Gaskell, and presents a very clear analysis of the much discussed doctrines dealing with the neurogenic and myogenic theories of cardiac function. If we were to venture any criticism of the author's treatment of this phase of the subject, it would be that we fear lest, by the very necessity of the method followed in his analysis of the various functions of cardiac muscle, he has conveyed the impression of an apparent interdependence of physiological function which actually does not exist to the degree suggested by the text.

The cardiac irregularites are discussed in a very satisfactory way and are well illustrated by both polygraphic and electrocardiographic curves, a large number being taken, as the author states, from the writings of Lewis and Mackenzie, to which are added many of his own records.

Short chapters on the systolic murmur and the principles of treatment conclude the volume, the value of which is not a little enhanced by a most satisfactory index.

This is a work which it is a genuine pleasure to commend, quite as much for the way in which the subject matter is presented as for the soundness of the views expressed. It is interesting, as illustrating the rapid advances of our knowledge, that even in this book, though bearing the date of 1921, there is no allusion to the modern theory of the "circus movement" in the description of auricular flutter and fibrillation.

We are confident that a second edition will soon be called for in which the more recent contributions of Lewis and his coworkers will be incorporated; and may we venture to add the hope that reference to the work of Einthoven and Hugenholz and to that of Arbeiter, in connection with the subject of electrical and mechanical phenomena, may find a place in any subsequent revision.

E. P. C.

Tuberculosis in Infancy and Childhood. By J. Claxton Gittings, M. D., Frank Crozer Knowles, M. D. and Astley P. D. Ashhurst, M. D. Cloth, $5.00. (*Philadelphia and London, J. B. Lippincott Company, 1922.*)

The authors approach the subject of tuberculosis from the point of view of the pediatrician. In most text-books on pediatrics, a proportionately large space is devoted to tuberculosis, but in such books the really detailed information that is often required is apt to be missing. This volume fills a definite need in furnishing such information in a concise but comprehensive manner, and in presenting impartially a summary of our present knowledge of tuberculosis, as it occurs in infancy and childhood. In several respects it illustrates the changing attitude of pediatricians in regard to the prognosis in tuberculosis, in pointing out that the mortality in infancy, although very high, is distinctly lower than was formerly believed. This change in attitude is due largely to the increased use of well defined methods of diagnosis, chiefly the intradermal tuberculin test. The chapter on the use of Tuberculin in diagnosis is particularly well presented. The authors stress the point to which all pediatricians bear witness; namely, that until in the most advanced stages tuberculosis in infants often does not interfere noticeably with the general nutrition.

The book is well arranged. The few illustrations are very good, but add little to its value.

B. T.

The Blood Supply to the Heart in its Anatomical and Clinical Aspects. By Louis Gross, M. D., C. M. Cloth, $5.00. (*Paul B. Hoeber, New York, 1921.*)

This monograph presenting the results of the author's researches upon the structural evolution of the circulation of the heart, based upon an exhaustive study of one hundred hearts of all age periods, is a very valuable contribution, and illustrates in a striking way the important clinical application of a study primarily undertaken as a purely anatomical investigation. After describing briefly the technical methods used by previous investigators, the author discusses the difficulties involved in any attempt to inject the coronary circulation, and describes in detail the technique followed in his method of procedure. He then discusses the vascular supply to the auricles and ventricles and summarizes the circulation to the heart as a whole, emphasizing the fact that, although there can be no hard and fast line of demarcation between the distribution of the right and left coronary arteries, which, as he has shown, have profuse and abundant anastomoses, it is quite possible to adopt an arbitrary division, with certain overlapping territory, which permits of an accurate description of the distribution of the coronary circulation in the average heart. He classifies by means of tables and text all the most important deviations from the usual in his series of hearts.

We have been particularly interested in the account of the blood supply to the neuro-muscular tissue, and have been greatly impressed by the evidence adduced to show that there exists a specific vascular supply for the sino-auricular node from the *Ramus ostii cavæ superioris* of the right coronary—occasionally arising from the left—and that there is no evidence for the opinion that anastomoses exist between the vessels supplying the sino-auricular and the auriculo-ventricular nodes; a view entirely confirming and amplifying the previous observations of Keith and Flack and of Koch. The author is of the opinion that a distinct and specific blood supply exists for both the sino-auricular and auriculo-ventricular nodes, the main stem of the His bundle, the first portion of the left branch and a large part of the right branch of the specialized conduction tissue—an anatomical difference of the greatest practical significance in our interpretation of lesions arising from any functional disturbance due to changes in the vascular supply. This is further emphasized by a brief discussion of a few instances from the series of cases reported by Moenckeberg. No more appealing brief for the necessity of an accurate correlation of our clinical and galvanometric observations with careful anatomical and injection studies could be offered than this chapter upon the blood supply to the neuromuscular system. The all too ready assumption of *post hoc propter hoc* plays often far too large a part in many utterly uncontrolled conclusions.

The question of the blood supply to the heart valves has been without doubt one of the most controversial fields of cardiac vascular morphology. Dividing the prevailing conflicting evidence into three main groups, the author concludes, as a result of experimental work and his interpretation of the literature, that each of these conflicting views may be in a measure correct, if not accepted in entirety, and that they can all be coordinated into a logical and reasonable explanation for the genesis of many cases of acute valvular endocarditis. In this connection the following paragraph may be quoted in full:

"If the literature on the mechanism of acute valvular endocarditis is now reviewed in this light, one is at once struck with the fact that the occurrence of endocarditis bears a strikingly close relationship to that of the existence of musculature and of blood vessels in valves. This becomes even more striking when the incidence of endocarditis is considered from the point of view of the frequency with which it occurs on the left and right sides as well as on the individual valves and cusps."

The author's premises in this connection based upon his experimental data, as given on page 71, are very interesting and suggestive, and impress one as being sound. We wish that we might quote at length from his discussion of the subject of anastomoses between the coronary arteries, but this chapter must be read in its entirety to be justly appreciated. His general conclusion that the heart is, perhaps, the richest organ in the body as regards capillary and precapillary anastomoses between branches of the same coronary artery, as well as between branches from both coronaries, seems to be abundantly supported on the basis of his available evidence and exhaustive study, and can but reinforce our conception of the marvellous provision for the maintenance of the normal anabolic and katabolic functions.

We know of no text which can in any sense be said to approach the careful detailed and concise outline covered by the author in his description of the venous circulation of the heart. The concluding chapter, dealing with the age period changes in the blood supply and their pathogenic relations, furnishes a most stimulating and suggestive discussion based upon a broad biological consideration of all the factors at work in the postnatal evolution of the individual. The volume is illustrated throughout with really remarkable plates and its value as a work of reference is tremendously increased by the exhaustive bibliography and by an index of authors, as well as an unusually satisfactory index of subjects. E. P. C.

Obstetrical Nursing. A Text-book on the Nursing Care of the Expectant Mother, the Woman in Labor, the Young Mother and Her Baby. By CAROLYN CONANT VAN BLARCOM, R. N. (*The Macmillan Company, New York, N. Y.*) ($3.00)

Examination of many of the text-books of obstetrics for nurses shows that most of them present the subject inadequately and make little attempt to elevate the art of midwifery to the science of obstetrics. Some are so antiquated and scientifically inaccurate that they are of little value. In many instances the attempts at brevity so limit description of the methods employed in the various clinics as to restrict their use to the hospitals from which they originated.

It is a pleasure to welcome a book which has overcome most of these objections. Miss Van Blarcom takes the stand that the obstetrical nurse is more useful if she understands more than the nursing care of her patients. Therefore, the anatomy, physiology and pathology of pregnancy, labor, the puerperium and the newborn child are adequately and simply explained. The author has familiarized herself with the obstetrical procedures of the leading hospitals of this country and Canada, and this broad view is reflected in her book. It gives the nurse a much clearer understanding of the subject and prepares her for the varying practices with which she may meet in her work. The nursing care of the mother and child is presented in a manner quite different from usual. While the various procedures employed in the better hospitals are described in detail, it is recognized that many women are delivered at home and that the nurse must often work with inadequate equipment. To meet this need, therefore, the author has simplified, as far as possible, the routine hospital procedures.

The author is to be commended especially for including in her book many of the modern ideas concerning prenatal care, the mental hygiene of the expectant mother and the nutrition of the mother and child. These chapters are among the best in the book and add much to its value. Incidentally, much of this subject matter might well be incorporated in the texts for medical students and practitioners.

Throughout the book sustained effort is made to impress the nurse with the fact that she is dealing with an individual rather than with a "case," that her patient is going through the most eventful period of her life, many of whose phenomena she does not understand, and that thoughtful sympathy on the part of the nurse is as much her duty as the actual nursing care of the patient.

The book is written in an interesting and simple style, and the text is clarified by numerous excellent photographs, drawings and charts. It adequately fills a real need in the teaching and training of nurses. J. W. H.

Management of the Sick Infant. By LANGLEY PORTER, M. D. and WILLIAM E. CARTER, M. D. Cloth, $7.50. (*St. Louis, C. V. Mosby and Company, 1922.*)

The authors have prepared a book that deals exclusively with the management of diseases peculiar to children and infants. The commoner symptoms of disease, such as convulsions, vomiting and so forth, their causes and methods of treatment are taken up in order. Following this, the disease entities of the different systems are similarly treated. At the end of the book there is a long list of prescriptions, which the authors have found useful. The chapter on the preparation of various food substances is particularly well arranged and should prove very helpful. The book is of use particularly to the practicing pediatrician and should be of value as a book of reference for any physician in his management of sick children.

There is nothing revolutionary or startlingly new in the volume. The authors have presented, in an exceptionally complete way, detailed directions for the management of all emergencies. B. T.

An Introduction to the Study of the Protozoa, with Special Reference to the Parasitic Forms. By E. A. MINCHIN. Second Impression. Cloth, $8.50. (*London, Edward Arnold, 1922.*)

Professor Minchin, whose researches have added many important contributions to the knowledge of zoology, was elected Professor of Protozoology in the University of London in 1906. While there, he wrote this book, which was recognized at once to be a masterful, lucid, and readable presentation of all the main facts about the structure and classification of the protozoa.

Since its publication in 1913, the book has been of great use to all students of systematic protozoology and also to those more directly concerned with the medical aspect of the subject. It attempts to determine the position of the *Protozoa* in nature. To guide the student through the technicalities of the study, all technical terms are defined and explained. While the mutual affinities and interrelationships of these organisms are expressed in as rigid a classification as possible, the author discusses philosophically those parts of the subject where *Protozoa* "throw great light on some of the fundamental mysteries of living matter—as for example, sex—and a special chapter dealing with the physiology of the *Protozoa* has been added."

The author states in his preface that as he is "not a medical man.... purely medical problems.... as the symptoms and treatment of diseases caused by the *Protozoa*—are not dealt with in this book. The needs of the medical men have, however, been specially kept in view, and the author hopes that the book will succeed in supplying them with useful information, at least from a general zoological or biological standpoint." From this point of view, the reviewer finds that the section of the book dealing with the trypanosomes and allied parasites is the most satisfactory.

In 1915, Professor Minchin died. The volume just issued from the press is an unrevised reprint of the first edition published in 1913. It lacks, therefore, the completeness which it would have had if its author had lived to add to it the knowledge of the protozoa which has been established during the last nine years. In spite of that deficiency, it remains the best book in English on this subject. S. B. J.

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